applied sciences

MDPI

Systematic Review

Therapeutic Advances in Tendinopathy Quantified Microscopically Using Bonar Score, with a Special Reference to PRP Therapy—A Systematic Review of Experimental Studies

Jan Zabrzyński [1,2,3,*], Maciej Gagat [4], Gazi Huri [5], Łukasz Łapaj [1], Łukasz Paczesny [2], Wioletta Zielińska [4], Maria Zabrzyńska [6], Dawid Szwedowski [2] and Jacek Kruczyński [1]

1 Department of General Orthopaedics, Musculoskeletal Oncology and Trauma Surgery, University of Medical Sciences, 61-701 Poznan, Poland; esperal@o2.pl (Ł.Ł.); jacek@man.poznan.pl (J.K.)
2 Department of Orthopaedics, Orvit Clinic, Citomed Healthcare Center, 87-100 Torun, Poland; drpaczesny@gmail.com (Ł.P.); dszwedow@yahoo.com (D.S.)
3 Department of Pathology, Faculty of Medicine, Nicolaus Copernicus University in Torun, 87-100 Torun, Poland
4 Department of Histology and Embryology, Faculty of Medicine, Nicolaus Copernicus University in Torun, 87-100 Torun, Poland; mgagat@cm.umk.pl (M.G.); w.zielinska@cm.umk.pl (W.Z.)
5 Orthopaedics and Traumatology Department, Hacettepe Universitesi, Ankara 06-352, Turkey; gazihuri@yahoo.com
6 Faculty of Medicine, Nicolaus Copernicus University in Torun, Collegium Medicum in Bydgoszcz, 87-100 Torun, Poland; maria.zabrzynska@gmail.com
* Correspondence: jan.zabrzynski@cm.umk.pl

Abstract: (1) Background: The Bonar scoring system serves in the microscopic evaluation of tendon pathology. However, it can be easily adapted to investigate decreasing degeneration after treatment and quantify the healing progress. We believe that there is an actual need for a connection between clinical observations and tissue alterations arising during the treatment process, to gain superior functional outcomes. Herein, we perform a systematic review of the Bonar score's application in the histopathological assessment of therapeutic advances in tendinopathy, with special reference to PRP therapy. (2) Methods: A systematic review was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The searching strategy was conducted across major databases: PubMed, Cochrane Central, ScienceDirect, SciELO, and Web of Science. The risk-of-bias assessment was made using the Cochrane Collaboration's Risk of Bias Tool and SYRCLE. (3) Results: The searching strategy produced 807 articles, and after selection, 22 studies were included. We collected 21 animal studies (n = 472) and 1 human study (n = 45). Three types of tendons were taken into account: 14 Achilles tendons, 7 supraspinatus tendons (SST), and in 1 case, Achilles and patellar tendons simultaneously. A variety of therapeutic methods were used—from intra-tendinous substance injections to surgical procedures or mechanical stimuli—but platelet-rich plasma (PRP) therapy dominated among them and was present in six studies. Most of the collected studies included an assessment of the tendons' histopathology based on the classical Bonar score (with four variables and one observer). The staining protocol was based on the hematoxylin and eosin technique. An evaluation of therapeutic effects showed 15 positive results, 6 negative results, and 1 neutral result of treatments. (4) Conclusions: To understand the tendinopathy phenomenon, a link between histopathology and clinical observations in chronic tendon disorders is required due to the possibility of functional outcome improvements. The Bonar scoring system is well established in tendon pathology assessment and could also be adopted to assess therapeutic results in tendon disorders. Studies that included the PRP application showed Bonar-scoring-system-based evidence of superior tendinous tissue healing related to improved clinical results.

Keywords: Bonar; tendon; tendinopathy; therapeutic advances; PRP; orthobiology

Citation: Zabrzyński, J.; Gagat, M.; Huri, G.; Łapaj, Ł.; Paczesny, Ł.; Zielińska, W.; Zabrzyńska, M.; Szwedowski, D.; Kruczyński, J. Therapeutic Advances in Tendinopathy Quantified Microscopically Using Bonar Score, with a Special Reference to PRP Therapy—A Systematic Review of Experimental Studies. *Appl. Sci.* **2021**, *11*, 4973. https://doi.org/10.3390/app11114973

Academic Editors: Luca Testarelli and Suwan N. Jayasinghe

Received: 1 May 2021
Accepted: 25 May 2021
Published: 28 May 2021

1. Introduction

Acute injuries of the tendons are among the most common in the human body [1]. The injured tendon healing process consists of three main phases, which are essential for soft tissue healing. However, in the case of an incomplete healing process, degeneration of the tissue may occur [2]. The tendinopathy process is characterized by the uncontrolled production of both collagenous and non-collagenous extracellular matrix (ECM), apoptosis in the local fibroblast population, and chaotic invasion of newly formed capillaries [2–8]. These histopathological alterations are reflected in decreased mechanical durability of the tendon and clinically manifest as tendinopathy. The healing of the injured tendon is conducted by a complex network of cytokines and mediators, which dynamically interact during regeneration of the tendinous tissue. This can be used in the therapy of tendon disorders [2,9]. The presence of specific types of growth factors in adequate time is crucial to fully recovering the tissue [2,9–11]. Many agents, such as mesenchymal stem cells (MSCs), growth factors, and hemostatic agents, have been studied to improve the tendon healing process [4,12–15].

It is currently believed that five main growth factors play a crucial role in the tendon healing process: insulin-like growth factor-1 (IGF-1), transforming growth factor-β (TGF-β), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and basic fibroblast growth factor (bFGF). Further, all of them are included in platelet-rich plasma (PRP). This is an autologous plasma fraction with a platelet-rich cellular component containing growth factors in alpha granules [16]. The efficacy of platelet concentrates in promoting wound healing and tissue regeneration is at the center of a recent academic debate [17]. Some authors even tried this therapy in osteonecrosis; however, the results are not sufficient to establish this method as a gold standard [18]. Moreover, the regeneration process demands cells to supply the local fibroblast population responsible for extracellular matrix production [2]. Recent studies revealed the positive role of MSCs, which are the progenitors for the fibroblast population, in tendon injury therapy [19–21]. Moreover, Vigano et al. suggested that autologous microfragmented adipose tissue reduces the inflammatory and catabolic markers in tenocytes [22]. Other authors isolated the extracellular vesicles from human adipose-derived MSCs to develop new therapeutic approaches in osteoarthritis [23].

The most common and well-established system to quantify the pathological changes in tendinous tissue is the Bonar scale [24,25]. The Bonar scoring system is based on four main variables: tenocyte morphology, ground substance accumulation, the extent of the neovascularization process, and the disruption of the collagen bundle architecture. Each variable is assessed on the scale of 0 to 3 points, where 0 indicates a normal appearance of tendinous tissue and 3 indicates the most severe detectable pathology [24]. The Bonar scoring system serves in the microscopic evaluation of the various regions of tendon pathology, but on the other side, it can be easily used reversely to investigate the decreasing degeneration after effective treatment and quantify the healing progress [24,26–30]. The link between the histopathological scale and therapeutic advances of various treatment methods in chronic tendon disorders has been evaluated in only a few studies. Despite the numerous reports about improved clinical conditions after tendon treatment based on functional scales, surprisingly, the microscopic state of the tissue was not assessed [31,32]. We believe that there is a real need for a connection between clinical observations and tissue alterations arising during the treatment, to gain superior functional outcomes.

This study was aimed to perform a comprehensive, systematic review of the Bonar score's application in the histopathological assessment of therapeutic advances in tendinopathy, focusing on PRP therapy.

2. Material and Methods

2.1. Search Strategy

A systematic review of the collected literature was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines

(Supplementary Material) [33]. To identify all of the essential studies that reported relevant information and data concerning therapy in tendon disorders quantified using the Bonar scale, an extensive search of the major and significant electronic databases (PubMed, Cochrane Central, ScienceDirect, SciELO, and Web of Science) was performed. A systematic investigation was conducted in February 2021, using combinations of the key terms "Bonar tendon" OR "Bonar tendinopathy" OR "Bonar score", with no limits regarding the year of publication. Moreover, an additional intensive search through the references of all identified studies was conducted.

2.2. Eligibility Assessment

The search in databases was done by two authors (J.Z., M.G.), independently. Next, three independent reviewers (J.Z., D.S., M.G.) screened all the papers identified for a title, abstract, and full text concerning the application of the Bonar score in the evaluation of tendinopathy treatment. Preclinical and clinical human and animal studies in English were evaluated and analyzed in this systematic review. Non-English-language studies, case studies, reviews, letters to editors, conference abstracts, or studies containing incomplete or irrelevant data were not eligible for inclusion. We also excluded papers without clearly quantified tendon alterations using the Bonar score. Moreover, studies with no specific drugs or treatment methods were not taken into consideration. Additionally, we excluded Bonar score application in structures other than tendons, such as menisci. The senior author and expert in evidence-based medicine (M.G.) made the final decision if there was disagreement among the authors.

2.3. Data Extraction

Three independent reviewers (J.Z., M.G., D.S.) extracted the initially screened and relevant data, including the year of the study, country, type of the study, number of subjects, region of tendon, control group inclusion, applied Bonar score and its modifications, number of investigators, area of tendon investigation, staining methods, mean Bonar scores in the treated and control groups, and the applied therapeutic methods and their effects.

2.4. Risk-of-Bias Assessment

The risk-of-bias assessment was done using the two different scoring tools. The Cochrane Collaboration's Risk of Bias Tool was employed in this study for quality appraisal of the included human study paper [25]. Risk of bias was assigned to the following domains as 'low', 'high', or 'unclear': sequence generation/allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other sources of bias. Moreover, we used the SYRCLE (Systematic Review Centre for Laboratory animal Experimentation) Risk of Bias Tool in this study for quality appraisal of the included animal studies. The quality of papers was assessed independently by two reviewers, with agreement.

3. Results

The results of the literature search are presented in the PRISMA flow diagram (Figure 1). The general characteristics and demographic data are presented in Table 1.

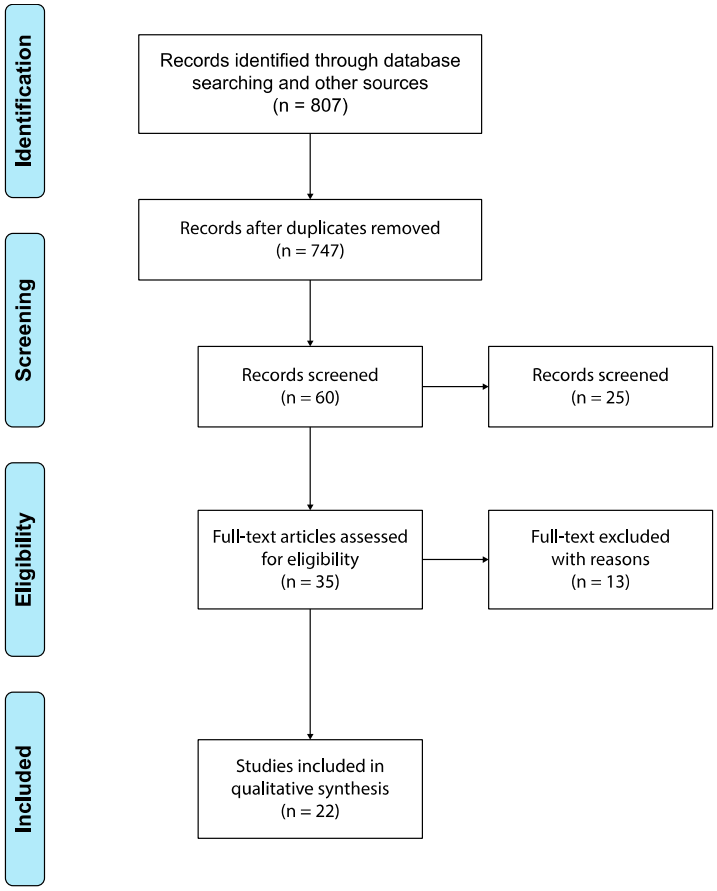

Figure 1. Flow diagram according to PRISMA.

3.1. Study Selection

This systematic review includes a total of 22 papers with a number of studied subjects of n = 517. We collected 21 animal studies (n = 472) and 1 human study (n = 45), the oldest of which was from 2007 and the most recent from 2020. The included studies originated from various countries, and the most common was Turkey (10 papers). Three types of tendons were taken into account: 14 Achilles tendons, 7 supraspinatus tendons (SST), and in 1 case, Achilles and patellar tendons simultaneously. The control group was included in all studies. There was a variety of therapeutic methods, from intra-tendinous substance injections to surgical procedure or mechanical stimuli, but PRP therapy dominated among them and was present in six studies. In Figures 2 and 3 we present the risk-of-bias assessment using graphs [54,55].

Table 1. Demographic data of collected studies with various therapeutic methods.

Author	Type of Study	Country	Year of Publication	Region of Tendinopathy	No. of Subjects	Control	Therapeutic Method
Fukawa et al. [16]	Animal in vivo study	Japan	2015	Achilles	24	√	PRP
Güleç et al. [1]	Animal in vivo study	Turkey	2018	Achilles	9	√	Curcumin
Beytemür et al. [34]	Animal Study	Turkey	2018	Achilles	8	√	Isotretinoin
Pingel et al. [35]	Animal in vivo study	Denmark	2013	Achilles	12	√	High-intensity training
Çıraklı et al. [36]	Animal in vivo study	Turkey	2018	Achilles	12	√	Tranexamic acid
de Cesar et al. [37]	Animal in vivo study	Brazil, USA	2018	Achilles	36	√	Collagenase
Genç et al. [38]	Animal in vivo study	Turkey	2018	Achilles	20	√	ACS (autologous conditioned serum)
Eren et al. [39]	Animal in vivo study	Tukey	2018	Achilles	24	√	LMWH/Rivaroxaban
Dincel et al. [40]	Animal in vivo study	Turkey	2018	Achilles	32	√	Vitamin C/Hyaluronic Acid
Aydın et al. [41]	Animal in vivo study	Turkey	2015	Achilles	12	√	Ankaferd blood stopper®
Kim et al. [42]	Animal in vivo study	Korea	2015	SST	21	√	PRP
Genç et al. [43]	Animal in vivo study	Turkey	2020	Achilles	20	√	PRP
Yoon et al. [44]	Animal in vivo study	Korea	2018	SST	48	√	TGF-B/Scaffold
Scott et al. [45]	Animal in vivo study	Canada	2007	SST	23	√	IGF1
Dolkart et al. [46]	Animal in vivo study	Israel	2014	SST	22	√	PRP
Yüksel et al. [47]	Animal in vivo study	Turkey	2015	Achilles	10	√	PRP
Sun et al. [48]	Animal in vivo study	Korea	2020	SST	20	√	Subacromial bursa excision
Oztermeli et al. [49]	Animal in vivo study	Turkey	2019	SST	48	√	EPO
Pecin et al. [50]	Animal in vivo study	Croatia	2016	Achilles	13	√	Interleukin-1 receptor antagonist
Saha et al. [51]	Human in vivo study	India	2016	SST	45	√	PRP
Kokubu et al. [52]	Animal in vivo study	Japan	2020	Achilles	18	√	Adipose-derived Stem Cells
Dallaudière et al. [53]	Animal in vivo study	France	2013	Achilles and Patellar tendons	40	√	Bevacizumab

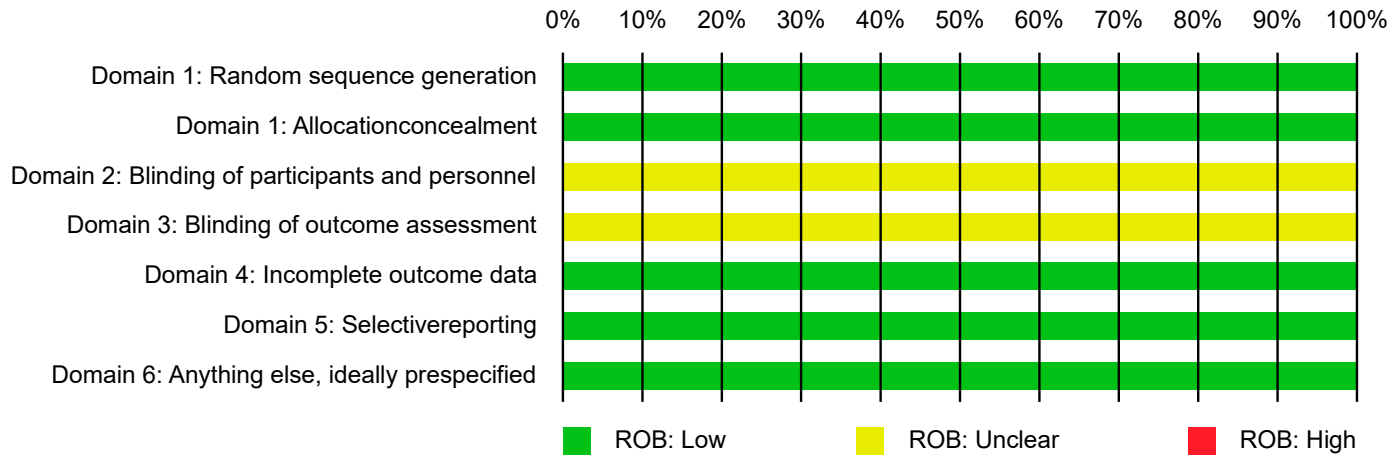

Figure 2. The risk-of-bias assessment graph using Cochrane Collaboration's Risk of Bias Tool dedicated for human studies (ROB, risk of bias).

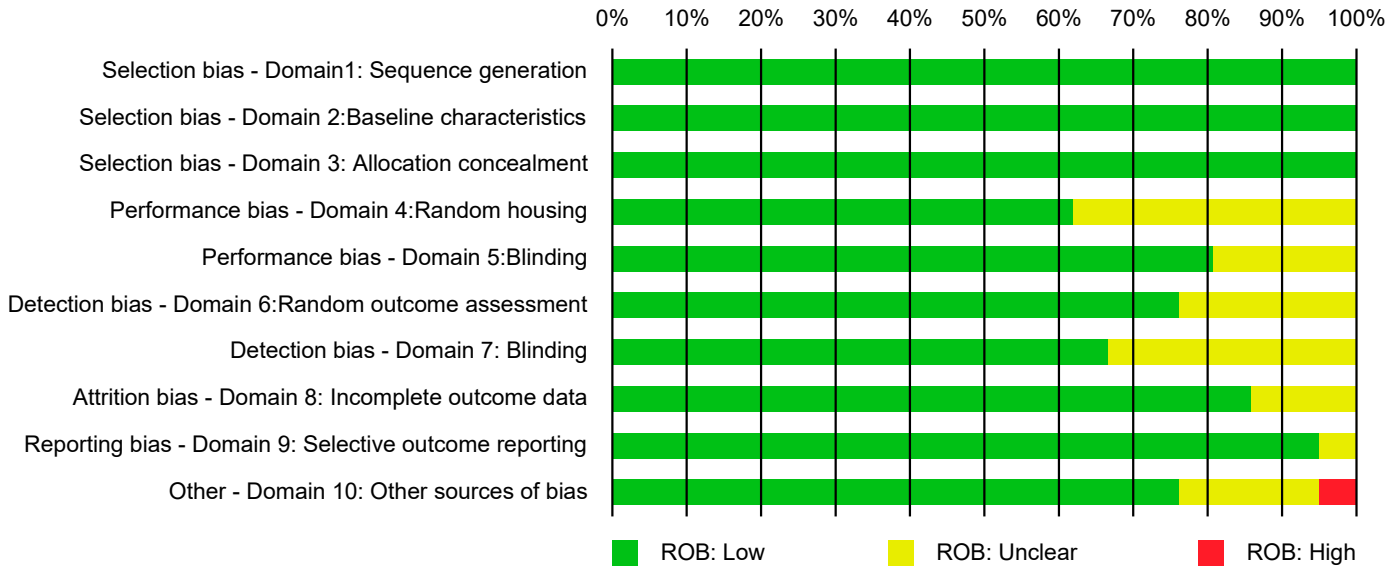

Figure 3. The risk-of-bias assessment graph using the SYRCLE Risk of Bias Tool dedicated for animal studies (ROB, risk of bias).

3.2. The Bonar Score and Its Modifications

Most of the collected studies included an assessment of the tendons' histopathology based on the classical Bonar score with four variables [1,16,34,36,38–44,46–53]. However, a few authors aimed to modify the classical assumptions of the scoring system in order to improve the diagnostics and microscopic evaluation. Pingel et al., de Cesar et al., and Scott et al. applied an additional variable based on the assessment of tenocyte proliferation [35,37,45]. Moreover, in six studies, the authors supported the histopathological evaluation with the Movin scoring system, which additionally includes the assessment of collagen fiber structure, decreased collagen stainability, hyalinization, and regional variations in cellularity [34,38–40,43,47].

3.3. Methodology of Microscopic Investigation

Regarding the number of investigators, the most common version was one observer. In three cases, there were two investigators [16,37,48] (Table 2).

Table 2. Methodology of microscopic investigation in the included studies.

Author	Components of Bonar Score	Number of Investigators	Area of Specimen Investigation	Additional Staining Methods
Fukawa et al. [16]	4 main	2	The most pathological area	Masson's Trichome
Güleç et al. [1]	4 main	1	n/a	Alcian Blue
Beytemür et al. [34]	4 main	n/a	n/a	Masson Trichrome, Alcian Blue
Çıraklı et al. [36]	4 main	1	n/a	Masson Trichrome, Alcian Blue
Genç et al. [38]	4 main	n/a	n/a	Masson Trichrome, Alcian Blue, Sirius Red, IHC
Eren et al. [39]	4 main	n/a	n/a	Masson Trichrome, Alcian Blue, Sirius Red
Dincel et al. [40]	4 main	n/a	n/a	Masson Trichrome, Alcian Blue
Aydın et al. [41]	4 main	1	n/a	Alcian Blue
Kim et al. [42]	4 main	1	n/a	Masson Trichrome, IHC
Genç et al. [43]	4 main	1	n/a	Masson Trichrome, Alcian Blue
Yoon et al. [44]	4 main	1	5 scanned sections per slide	Masson Trichrome, Alcian Blue, Pictorius Red, SafraninO
Dolkart et al. [46]	4 main	1	n/a	Alcian Blue, Picrosirius Red
Yüksel et al. [47]	4 main	1	n/a	Masson Trichrome, Alcian Blue
Sun et al. [48]	4 main	2	Total area of specimen	IHC
Oztermeli et al. [49]	4 main	1	n/a	Alcian Blue
Pecin et al. [50]	4 main	n/a	n/a	Masson Trichrome, Verhoeff van Gieso, Gridley method, Gomori method
Saha et al. [51]	4 main	n/a	n/a	n/a
Kokubu et al. [52]	4 main	n/a	n/a	Toluidine Blue, Alizarin Red
Dallaudière et al. [53]	4 main	n/a	n/a	Masson Trichrome
Pingel et al. [35]	4 main + tenocyte proliferation	1	n/a	Alcian Blue, IHC
de Cesar et al. [37]	4 main + tenocyte proliferation	2	The most pathological area	Alcian Blue, Safranin, Picrosirius Red
Scott et al. [45]	4 main + tenocyte proliferation	1	Total area of specimen	Alcian Blue, Picrosirius Red

However, in eight studies, there were no data concerning the number of microscopic examiners [34,38–40,50–53].

The standard staining protocol was based on hematoxylin and eosin, while the most popular additional staining method was Alcian Blue [1,34–41,43–47,49] The second most frequent method was Masson Trichrome [16,34,36,38–40,42–44,47,50]. Other staining methods, such as Picrosirius red Verhoeff van Gieso, Gridley method, Gomori method, Safranin, Toluidine Blue, and Alizarin Red, were rather rare [37,44]. In one paper, the authors did not use any additional staining [51]. In four studies, the authors augmented their histopathological methods with immunohistochemistry, such as collagen type I and III labeling [35,38,42,48].

The majority of studies did not present the exact area of microscopic investigation. On the other hand, two authors evaluated the total area of the specimen [45,48], and two others chose the most severely degenerated region of tendon specimens [16,37].

3.4. Therapeutic Effects

An evaluation of therapeutic effects showed 15 positive results [1,38–40,42–44,46–53], 6 negative results [34–37,41,45], and 1 neutral result of treatments [16] (Table 3).

Table 3. Therapeutic methods, clinical effects, and their influence on the Bonar score.

Author	Therapeutic Method	Therapeutic Effect	Mean Bonar Score	Mean Bonar Score Control Group	Comment on Therapeutic Advance
Fukawa et al. [16]	PRP	Neutral	8.3	8.9	No significant effect of PRP treatment on the T2 value in MRI or Bonar score was observed
Güleç et al. [1]	Curcumin	Positive	4.1	6.77	Curcumin application resulted in improved total tendon healing histologically and biomechanically
Beytemür et al. [34]	Isotretinoin	Negative	2.9	1.6	The study detected histopathological and biomechanical negative effect of isotretinoin on Achilles tendon healing
Pingel et al. [35]	High-intensity training	Negative	2.75	1.17	High-intensity training caused structural changes in the Achilles tendon and increased mast cell density
Çıraklı et al. [36]	Tranexamic acid	Negative	9.33	9.167	Locally administered tranexamic acid had an adverse effect on tendon healing
de Cesar et al. [37]	Collagenase (low dose)	Negative	11.8	5.6	Low dose Coll. specimens showed worse histological and biomechanical properties
Genç et al. [38]	ACS (autologous conditioned serum)	Positive	5.6	7	Injection of ACS had a positive effect on the histopathological healing of rat Achilles tendons on days 15 and 30, and on biomechanical healing on day 15
Eren et al. [39]	LMWH/Rivaroxaban	Positive	LMWH: 5.5 Rivaroxaban: 5.7	9	Both LMWH and rivaroxaban showed positive effects on tendon healing with no effect in biomechanical examination
Dincel et al. [40]	Vitamin C/Hyaluronic Acid	Positive	Vit. C: 8 HA: 8.7	10	Both vitamin C and hyaluronic acid had therapeutic effects on tendon healing
Aydın et al. [41]	Ankaferd blood stopper®	Negative	6.58	4.91	Application of ABS had histologically negative effect on tendon healing in rats
Kim et al. [42]	PRP	Positive	Self-assembled peptide (SAP): 6.4 PRP: 5.9 SAP+PRP: 4.7		SAP+PRP can be effective in healing a rotator cuff tear by enhancing the collagen arrangement, inhibiting inflammatory changes and apoptosis
Genç et al. [43]	PRP	Positive	ACS: 4.8 PRP: 3.8	5.2	PRP treatment after Achilles tendon surgery showed better histopathological results than both the ACS and control groups
Yoon et al. [44]	TGF-β/Scaffold	Positive	SST repair + TGF-B: 6.12 SST repair + TGF-B + Scaffold: 7.5	SST isolate repair: 5	Reverse Bonar score criteria improved biomechanical and histological outcomes after treatment with TGF-β/ scaffold and rotator cuff repair in a rabbit model.
Scott et al. [45]	Mechanical loading	Negative	5.2	0.9	In vivo tendon loading produced a non-inflammatory pathology

Table 3. *Cont.*

Author	Therapeutic Method	Therapeutic Effect	Mean Bonar Score	Mean Bonar Score Control Group	Comment on Therapeutic Advance
Dolkart et al. [46]	PRP	Positive	4.9	7.4	Bonar score of PRP-treated tendons was significantly improved ($p = 0.018$) compared with the control group. Vascularity scores were similar in both groups
Yüksel et al. [47]	PRP	Positive	3.25	6.25	PRP use in Achilles tendon ruptures positively affects histopathological recovery in the early period
Sun et al. [48]	Subacromial bursa excision	Positive	0.5	1.5	The modified Bonar scale scores showed improved regeneration of supraspinatus tendons in the bursal preservation group
Oztermeli et al. [49]	Erythropoietin (EPO)	Positive	Local EPO: 1.33 Systemic EPO: 4.5	6	EPO application showed better results in the late local group than the late systemic group. EPO may be an effective way to enhance rotator cuff repair
Pecin et al. [50]	Interleukin-1 receptor antagonist	Positive	1.5	2	Lower concentration of IL-1β prevented iatrogenic inflammation, which resulted in limited degeneration of tendons
Saha et al. [51]	PRP	Positive	2.3	7.31	Arthroscopic acromioplasty significantly limited symptoms of RCT. In combination with PRP, it significantly improved tendon healing
Kokubu et al. [52]	Adipose-derived Stem Cells (ASCs)	Positive	4.3	9.5	ASCs improved tendon repair and prevented ectopic ossification by inhibiting inflammation in acute tendon injury and inducing neovascularization in the early phase of tendon healing
Dallaudière et al. [53]	Bevacizumab	Positive	6	7	Intra-tendinous injection of Bevacizumab accelerated tendon healing on a rat model of tendinosis, with no local toxicity

The studies with positive therapeutic effects represented the following methods: curcumin application, autologous conditioned serum application, low-molecular-weight heparin and rivaroxaban injection, vitamin C and hyaluronic acid injection, TGF-β1 used with the scaffold, subacromial bursa excision, erythropoietin application, interleukin-1 receptor antagonist application, adipose-derived stem cell injection, bevacizumab application, and, in five studies, PRP application. The mean Bonar score in these studies was 0.5–8.7 points in the study group and 1.5–10 points in control subjects. The papers that revealed negative therapeutic effects used such methods as isotretinoin application, tranexamic acid injection, collagenase (low dose) injection, ankaferd blood stopper® application, mechanical loading, and high-intensity training application. The mean value of the Bonar score in the treated groups with negative results was 2.75–11.8 points, while in the control group, it varied between 0.9 and 9.167 points. One paper revealed a neutral effect of PRP injection, with a mean Bonar score in the study group of 8.3 points compared to 8.9 points in the control group.

4. Discussion

In this systematic review, we investigated papers where the Bonar histopathological score, designed primarily to evaluate excess tissue degeneration, was used in the assessment of therapeutic advances in tendinopathy. The Bonar scoring system, well known and established in the quantification of tendinous tissue degeneration, revealed a new attribute in all concerned studies—a function in the evaluation of tendon treatment effectiveness. We carefully selected 22 papers that mainly focused on PRP application in chronic tendon disorders, among which animal studies prevailed. However, the results of this systematic review showed that the Bonar score could also be easily applied in human in vivo studies to assess the shift of degeneration in healed tendinous tissue. Yet, there are some issues that have to be established and determined before widespread clinical application. The studies from the investigated papers were mainly focused on the Achilles, SST, and patellar tendons; however, the results of Bonar system use in the context of treatment results in other localizations, such as the posterior tibialis tendon (PTT), the long head of the biceps tendon (LHBT), and forearm tendons, are unknown. Further, a control group was presented in each paper and based mainly on Achilles tendon specimens. This is an important issue that is obligatory in the evaluation of various therapeutic methods in chronic tendon disorders. Future human studies should also have well-standardized control groups to easier define the therapeutic effect. Finally, the treatment methods used in the selected studies varied, but PRP application predominated. Positive effects of therapeutic methods prevailed; however, in one paper, a neutral effect of PRP application was noted. We still need a standardization of PRP therapy to predict a clinical effect, but on the other hand, the presented studies revealed no side effects of this treatment method.

In recent decades, increasing concern with platelet-rich plasma injections in tendon disorders has been noted. PRP therapy is a relatively inexpensive and easy-to-prepare procedure. PRP is widely used in different fields of medicine; however, the evidence base for the clinical use of PRP is still in its infancy [51]. This therapeutic method intends to augment the natural tendon healing process, supplying the tissue with specific, highly concentrated growth factors. PRP has been recommended as a treatment option in refractory tendinopathies [30]. Its injections into the patellar tendon, Achilles tendon, and tendons of digit flexors after injury have shown positive clinical results and led to superior regeneration [56]. The application of PRP in elbow tendinopathy showed promising results both radiologically and clinically [57,58]. On the contrary, some authors revealed no functional improvement among patients who underwent PRP therapy [59]. In such situations, histopathological assessment could be helpful to augment the functional evaluation of therapeutic results.

The authors of five of the six PRP studies evaluated in this systematic review showed that PRP had a positive effect on both clinical presentation and histopathology, including collagen architecture, ECM composition, tenocyte morphology, and expansion of capillaries.

Moreover, Kim et al. revealed that PRP therapy decreased inflammation and reduced the apoptosis rate in tendinous tissue [42]. On the other hand, a study by Fukawa et al. showed that there was no statistically significant improvement after Achilles tendon PRP treatment [16]. PRP application as a therapeutic method in chronic tendon disorders was the most widely used in the selected group of papers. However, there were other methods with a negative or positive effect on tendinous tissue. Güleç et al. used curcumin, Eren et al. used LMWH and rivaroxaban, Dincel et al. used vitamin C and hyaluronic acid, and Dallaudière et al. used Bevacizumab in Achilles tendon therapy; all authors observed improved regeneration of the tissue, established by the Bonar scoring system [1,39,40,53]. Moreover, Yoon et al. observed superior biomechanical and histological outcomes in animals treated simultaneously with scaffold and TGF-β [44]. Kokubu et al. transplanted ASCs, as a progenitor population to fibroblasts, into the injury site and observed improved tendon repair and the prevention of ectopic ossification [52]. On the other hand, Pingel et al. and Scott et al. presented a negative influence on tendon regeneration of excessive stress and inferior histopathological outcomes measured using the Bonar system [35,45]. Further, Isotretinoin, Tranexamic acid, and a low dose of Collagenase showed a negative effect on the tendon healing process, leading to more advanced degeneration than that in control groups [34,36,37].

Regarding the applied evaluation method, most of the authors used the four-variable Bonar score. However, three authors introduced a fifth variable representing tenocyte proliferation and counted the number of tenocytes. This alteration was also used in the quantification of pathology in tendinous tissue with the Bonar scale; nevertheless, this fifth variable should be reconsidered in further human studies [60,61]. Unfortunately, the number of microscopic investigators in presented studies was often not available or it was a single observer. In the studies of degeneration supported with the Bonar scale, two observers or at least one experienced investigator ensure the objective assessment of tissue [25]. Still, it is not clear how it should be set for human studies. However, the use of two observers is the best solution to avoid bias. The majority of authors were unable to set a certain area of microscopic investigation. This problem was also met in studies of tendon pathology, and authors usually randomly selected the evaluated area of the slide.

Regarding additional staining, the most frequent were Alcian Blue and Masson Trichrome methods, which are used for better visualization of ECM alterations. These additional stainings facilitate microscopic assessment of the tendon structure; however, none of the authors proved the necessity of these upgrades.

The role that the neovascularization process plays in tendon degeneration and healing is ambiguous; thus, this variable in the Bonar scoring system should be treated with caution [62–64]. Kokubu et al. showed that ASCs induced the neovascularization process in the early phase of Achilles tendon healing [52]. Moreover, Dolkart et al. revealed similar scores for the neovascularization variable in both the PRP-treated group and the control group, despite the significant improvement in the overall Bonar score of subjects who underwent PRP treatment [46]. Furthermore, Oztermeli et al. noticed no statistically significant effect on vascularity in the early phase after local or systematic administration of EPO [49]. EPO is a strong proangiogenic agent, while angiogenesis is crucial in tendon healing. Authors in the late period observed statistically significant differences between locally injected EPO (0 points in Bonar) and both systematically injected EPO and the control group (both 1.33 points in Bonar). They suggested that local EPO administration contributes to vascularization in the late period. However, the vascularization score corresponded to randomly scattered, inconspicuous capillaries. It could be concluded that the EPO application provided a faster reorganization of the angiogenesis process in tendinous tissue. New vessel formation is a characteristic feature of the formation phase of the tendon regeneration process which lasts approximately from the 7–8th day until the third week. On the contrary, the invasion of new vessels is known as a typical sign of tendinopathy and often treated using sclerosing drugs [64]. In turn, Fearon et al. considered a complete lack of vascularity in tendinous tissue a pathology, which in their

modified Bonar score was rated equally as an abundant neovascularization process [25]. Summarizing, the role of neovascularization in tendinopathy should be reconsidered in the Bonar score as well as avascular regions.

This systematic review was limited by a number of factors. First, the methodology of the included studies, the number of investigators, and the observed specimen area were highly differentiated. Second, the applied therapeutic methods had various influences on tendon histopathology—positive, negative, or neutral—and depending on the alterations, authors scored the tissue using the Bonar system. As the application of this scoring system was not yet well established in the evaluation of tissue regeneration, the results may be biased. Third, in some studies, there was a lack of demographic data, and the study design and methodology may have a significant impact on the interpretation of the results. We supported two well-established tools to minimalize the risk of bias; however, we realize that there are various scales used in the assessment of paper quality. In the majority of the included studies, we observed an overall low risk of bias; however, some studies presented limitations with unclear risk of bias, such as blinding, random housing, and random outcome assessment. Moreover, in one study we observed high risk of bias due to a lack of clarity in the presentation of results and figures.

5. Conclusions

The Bonar scoring system is well established in tendon pathology assessment and could also be introduced to assess therapeutic results in tendon disorders. To understand the tendinopathy phenomenon, a link between the histopathology and clinical presentation in chronic tendon disorders is required as it may improve functional outcomes. Studies that included PRP application showed evidence of superior tendinous tissue healing, measured using the Bonar score, and improved clinical results. Finally, there are some issues, such as the neovascularization variable in the scoring system, the number of investigators, the area of tissue investigation, specific staining methods, and control groups, that should be reconsidered and set before widespread clinical application. Further randomized clinical studies are needed to confirm these promising results.

Author Contributions: Conceptualization, J.Z.; methodology, J.Z., M.G., D.S.; software, J.Z., Ł.P.; validation, J.Z., M.G., Ł.Ł.; formal analysis, J.Z., Ł.Ł., M.G.; investigation, J.Z., D.S., M.G., M.Z.; resources, J.Z.; data curation, J.Z.; writing—original draft preparation, J.Z., M.G.; writing—review and editing, J.Z., D.S., W.Z., M.G.; visualization, J.Z.; supervision, J.K., ŁP., Ł.Ł, G.H.; project administration, J.Z.; funding acquisition, none. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: None.

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

Abbreviations

ACS	autologous conditioned serum
bFGF	basic fibroblast growth factor
IGF	insulin-like growth factor-1
ECM	extracellular matrix
EPO	erythropoietin
LHBT	the long head of the biceps tendon

LMWH	low-molecular-weight heparin
MSC	mesenchymal stem cells
PDGF	platelet-derived growth factor
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRP	platelet-rich plasma
PTT	posterior tibialis tendon
SST	supraspinatus tendon
SYRCLE	Systematic Review Centre for Laboratory animal Experimentation
TGF-β	transforming growth factor-β
VEGF	vascular endothelial growth factor

References

1. Güleç, A.; Türk, Y.; Aydin, B.K.; Erkoçak, Ö.F.; Safalı, S.; Ugurluoglu, C. Effect of curcumin on tendon healing: An experimental study in a rat model of Achilles tendon injury. *Int. Orthop.* **2018**, *42*, 1905–1910. [CrossRef]
2. Zabrzyński, J.; Łapaj, Ł.; Paczesny, Ł.; Zabrzyńska, A.; Grzanka, D. Tendon—Function-related structure, simple healing process and mysterious ageing. *Folia Morphol.* **2018**, *77*, 416–427. [CrossRef] [PubMed]
3. Riley, G. The pathogenesis of tendinopathy. A molecular perspective. *Rheumatology* **2003**, *43*, 131–142. [CrossRef]
4. Kaux, J.-F.; Forthomme, B.; Le Goff, C.; Crielaard, J.-M.; Croisier, J.-L. Current Opinions on Tendinopathy. *J. Sports Sci. Med.* **2011**, *10*, 238–253.
5. Abate, M.; Gravare-Silbernagel, K.; Siljeholm, C.; Di Iorio, A.; De Amicis, D.; Salini, V.; Werner, S.; Paganelli, R. Pathogenesis of tendinopathies: Inflammation or degeneration? *Arthritis Res. Ther.* **2009**, *11*, 235. [CrossRef] [PubMed]
6. Scott, A.; Backman, L.J.; Speed, C. Tendinopathy: Update on Pathophysiology. *J. Orthop. Sports Phys. Ther.* **2015**, *45*, 833–841. [CrossRef] [PubMed]
7. Zabrzyński, J.; Gagat, M.; Paczesny, Ł.; Łapaj, Ł.; Grzanka, D. Electron microscope study of the advanced tendinopathy process of the long head of the biceps brachii tendon treated arthroscopically. *Folia Morphol.* **2018**, *77*, 371–377. [CrossRef]
8. Zabrzyński, J.; Paczesny, Ł.; Łapaj, Ł.; Grzanka, D.; Szukalski, J. Process of neovascularisation compared with pain intensity in tendinopathy of the long head of the biceps brachii tendon associated with concomitant shoulder disorders, after arthroscopic treatment. Microscopic evaluation supported by immunohistochemical. *Folia Morphol.* **2018**, *77*, 378–385. [CrossRef]
9. Molloy, T.; Wang, Y.; Murrell, G.A.C. The Roles of Growth Factors in Tendon and Ligament Healing. *Sports Med.* **2003**, *33*, 381–394. [CrossRef] [PubMed]
10. Murphy, P.G.; Loitz, B.J.; Frank, C.B.; Hart, D.A. Influence of exogenous growth factors on the synthesis and secretion of collagen types I and III by explants of normal and healing rabbit ligaments. *Biochem. Cell Biol.* **1994**, *72*, 403–409. [CrossRef]
11. Evans, C.H. Cytokines and the Role They Play in the Healing of Ligaments and Tendons. *Sports Med.* **1999**, *28*, 71–76. [CrossRef]
12. Yin, Z.; Chen, X.; Zhu, T.; Hu, J.-J.; Song, H.-X.; Shen, W.-L.; Jiang, L.-Y.; Heng, B.C.; Ji, J.-F.; Ouyang, H.-W. The effect of decellularized matrices on human tendon stem/progenitor cell differentiation and tendon repair. *Acta Biomater.* **2013**, *9*, 9317–9329. [CrossRef]
13. Kaux, J.-F.; Drion, P.V.; Colige, A.; Pascon, F.; Libertiaux, V.; Hoffmann, A.; Janssen, L.; Heyers, A.; Nusgens, B.V.; Le Goff, C.; et al. Effects of platelet-rich plasma (PRP) on the healing of Achilles tendons of rats. *Wound Repair Regen.* **2012**, *20*, 748–756. [CrossRef]
14. Di Matteo, B.; Filardo, G.; Kon, E.; Marcacci, M. Platelet-rich plasma: Evidence for the treatment of patellar and Achilles tendinopathy—A systematic review. *Musculoskelet. Surg.* **2014**, *99*, 1–9. [CrossRef]
15. Usuelli, F.G.; Grassi, M.; Maccario, C.; Vigano, M.; Lanfranchi, L.; Montrasio, U.A.; de Girolamo, L. Intratendinous adipose-derived stromal vascular fraction (SVF) injection provides a safe, efficacious treatment for Achilles tendinopathy: Results of a randomized controlled clinical trial at a 6-month follow-up. *Knee Surg. Sports Traumatol. Arthrosc.* **2018**, *26*, 2000–2010. [CrossRef]
16. Fukawa, T.; Yamaguchi, S.; Watanabe, A.; Sasho, T.; Akagi, R.; Muramatsu, Y.; Akatsu, Y.; Katsuragi, J.; Endo, J.; Osone, F.; et al. Quantitative Assessment of Tendon Healing by Using MR T2 Mapping in a Rabbit Achilles Tendon Transection Model Treated with Platelet-rich Plasma. *Radiology* **2015**, *276*, 748–755. [CrossRef]
17. Bennardo, F.; Liborio, F.; Barone, S.; Antonelli, A.; Buffone, C.; Fortunato, L.; Giudice, A. Efficacy of platelet-rich fibrin compared with triamcinolone acetonide as injective therapy in the treatment of symptomatic oral lichen planus: A pilot study. *Clin. Oral Investig.* **2021**, *25*, 3747–3755. [CrossRef]
18. Fortunato, L.; Bennardo, F.; Buffone, C.; Giudice, A. Is the application of platelet concentrates effective in the prevention and treatment of medication-related osteonecrosis of the jaw? A systematic review. *J. Cranio Maxillofac. Surg.* **2020**, *48*, 268–285. [CrossRef]
19. Chaudhury, S. Mesenchymal stem cell applications to tendon healing. *Muscle Ligaments Tendons J.* **2012**, *2*, 222–229.
20. Awad, H.A.; Butler, D.L.; Boivin, G.P.; Smith, F.N.; Malaviya, P.; Huibregtse, B.; Caplan, A.I. Autologous Mesenchymal Stem Cell-Mediated Repair of Tendon. *Tissue Eng.* **1999**, *5*, 267–277. [CrossRef]
21. Selek, O.; Buluç, L.; Muezzinoğlu, B.; Ergün, R.E.; Ayhan, S.; Karaöz, E. Mesenchymal stem cell application improves tendon healing via anti-apoptotic effect (Animal study). *Acta Orthop. Traumatol. Turc.* **2014**, *48*, 187–195. [CrossRef]

22. Viganò, M.; Lugano, G.; Orfei, C.P.; Menon, A.; Ragni, E.; Colombini, A.; De Luca, P.; Randelli, P.; De Girolamo, L. Autologous microfragmented adipose tissue reduces inflammatory and catabolic markers in supraspinatus tendon cells derived from patients affected by rotator cuff tears. *Int. Orthop.* **2021**, *45*, 419–426. [CrossRef]
23. Tofiño-Vian, M.; Guillén, M.I.; Del Caz, M.D.P.; Silvestre, A.; Alcaraz, M.J. Microvesicles from Human Adipose Tissue-Derived Mesenchymal Stem Cells as a New Protective Strategy in Osteoarthritic Chondrocytes. *Cell. Physiol. Biochem.* **2018**, *47*, 11–25. [CrossRef]
24. Maffulli, N.; Longo, U.G.; Franceschi, F.; Rabitti, C.; Denaro, V. Movin and Bonar Scores Assess the Same Characteristics of Tendon Histology. *Clin. Orthop. Relat. Res.* **2008**, *466*, 1605–1611. [CrossRef]
25. Fearon, A.; Dahlstrom, J.E.; Twin, J.; Cook, J.; Scott, A. The Bonar score revisited: Region of evaluation significantly influences the standardized assessment of tendon degeneration. *J. Sci. Med. Sport* **2014**, *17*, 346–350. [CrossRef] [PubMed]
26. Sethi, P.M.; Sheth, C.D.; Pauzenberger, L.; McCarthy, M.B.R.; Cote, M.P.; Soneson, E.; Miller, S.; Mazzocca, A.D. Macroscopic Rotator Cuff Tendinopathy and Histopathology Do Not Predict Repair Outcomes of Rotator Cuff Tears. *Am. J. Sports Med.* **2018**, *46*, 779–785. [CrossRef]
27. Is the Inflammation Process Absolutely Absent in Tendinopathy of the Long Head of the Biceps Tendon? Histopathologic Study of the Long Head of the of the Biceps Tendon after Arthroscopic Treatment. 2020. Available online: https://www.ncbi.nlm.nih.gov/pubmed/29517202 (accessed on 3 January 2020).
28. Lundgreen, K.; Lian, Ø.B.; Scott, A.; Fearon, A.; Engebretsen, L. 58 Smokers Have Worse Rotator Cuff Teartendon Degeneration and Apoptosis. *Br. J. Sports Med.* **2014**, *48*, A37–A38. [CrossRef]
29. Singaraju, V.M.; Kang, R.W.; Yanke, A.B.; McNickle, A.G.; Lewis, P.B.; Wang, V.M.; Williams, J.M.; Chubinskaya, S.; Romeo, A.A.; Cole, B.J. Biceps tendinitis in chronic rotator cuff tears: A histologic perspective. *J. Shoulder Elb. Surg.* **2008**, *17*, 898–904. [CrossRef]
30. Cook, J.L.; Feller, J.A.; Bonar, S.F.; Khan, K.M. Abnormal tenocyte morphology is more prevalent than collagen disruption in asymptomatic athletes' patellar tendons. *J. Orthop. Res.* **2004**, *22*, 334–338. [CrossRef]
31. Aspenberg, P. Stimulation of tendon repair: Mechanical loading, GDFs and platelets. A mini-review. *Int. Orthop.* **2007**, *31*, 783–789. [CrossRef]
32. Li, H.-Y.; Hua, Y.-H. Achilles Tendinopathy: Current Concepts about the Basic Science and Clinical Treatments. *BioMed Res. Int.* **2016**, *2016*, 1–9. [CrossRef]
33. Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Brennan, S.E.; et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *PLoS Med.* **2021**, *18*, e1003583. [CrossRef]
34. Beytemür, O.; Yüksel, S.; Tetikkurt, Ü.S.; Genç, E.; Olcay, E.; Güleç, A. Isotretinoin induced achilles tendinopathy: Histopathological and biomechanical evaluation on rats. *Acta Orthop. Traumatol. Turc.* **2018**, *52*, 387–391. [CrossRef]
35. Pingel, J.; Wienecke, J.; Kongsgaard, M.; Behzad, H.; Abraham, T.; Langberg, H.; Scott, A. Increased mast cell numbers in a calcaneal tendon overuse model. *Scand. J. Med. Sci. Sports* **2013**, *23*, e353–e360. [CrossRef]
36. Çıraklı, A. Local application of tranexamic acid affects tendon healing negatively in the late period. *Jt. Dis. Relat. Surg.* **2018**, *29*, 20–26. [CrossRef]
37. Netto, C.D.C.; Godoy-Santos, A.L.; Pontin, P.A.; Natalino, R.J.M.; Pereira, C.A.M.; Lima, F.D.D.O.; Da Fonseca, L.F.; Staggers, J.R.; Cavinatto, L.M.; Schon, L.C.; et al. Novel animal model for Achilles tendinopathy: Controlled experimental study of serial injections of collagenase in rabbits. *PLoS ONE* **2018**, *13*, e0192769. [CrossRef]
38. Genç, E.; Beytemür, O.; Yüksel, S.; Eren, Y.; Çağlar, A.; Küçükyıldırım, B.O.; Gulec, M.A. Investigation of the biomechanical and histopathological effects of autologous conditioned serum on healing of Achilles tendon. *Acta Orthop. Traumatol. Turc.* **2018**, *52*, 226–231. [CrossRef]
39. Eren, Y. Effects of low molecular weight heparin and rivaroxaban on rat Achilles tendon healing. *Jt. Dis. Relat. Surg.* **2018**, *29*, 13–19. [CrossRef]
40. Dincel, Y.M.; Adanir, O.; Arikan, Y.; Caglar, A.K.; Dogru, S.C.; Arslan, Y.Z. Effects of high-dose vitamin C and hyaluronic acid on tendon healing. *Acta Ortopédica Bras.* **2018**, *26*, 82–85. [CrossRef]
41. Aydın, B.K. Effect of Ankaferd blood stopper®on tendon healing: An experimental study in a rat model of Achilles tendon injury. *Jt. Dis. Relat. Surg.* **2015**, *26*, 31–37. [CrossRef]
42. Kim, S.J.; Lee, S.M.; Kim, J.E.; Kim, S.H.; Jung, Y. Effect of platelet-rich plasma with self-assembled peptide on the rotator cuff tear model in rat. *J. Tissue Eng. Regen. Med.* **2015**, *11*, 77–85. [CrossRef]
43. Genc, E.; Yuksel, S.; Caglar, A.; Beytemur, O.; Gulec, M.A. Comparison on effects of platelet-rich plasma versus autologous conditioned serum on Achilles tendon healing in a rat model. *Acta Orthop. Traumatol. Turc.* **2020**, *54*, 438–444. [CrossRef]
44. Yoon, J.P.; Lee, C.-H.; Jung, J.W.; Lee, H.-J.; Lee, Y.-S.; Kim, J.-Y.; Park, G.Y.; Choi, J.H.; Chung, S.W. Sustained Delivery of Transforming Growth Factor β1 by Use of Absorbable Alginate Scaffold Enhances Rotator Cuff Healing in a Rabbit Model. *Am. J. Sports Med.* **2018**, *46*, 1441–1450. [CrossRef]
45. Scott, A.; Cook, J.L.; Hart, D.A.; Walker, D.C.; Duronio, V.; Khan, K.M. Tenocyte responses to mechanical loading in vivo: A role for local insulin-like growth factor 1 signaling in early tendinosis in rats. *Arthritis Rheum.* **2007**, *56*, 871–881. [CrossRef]

46. Dolkart, O.; Chechik, O.; Zarfati, Y.; Brosh, T.; Alhajajra, F.; Maman, E. A single dose of platelet-rich plasma improves the organization and strength of a surgically repaired rotator cuff tendon in rats. *Arch. Orthop. Trauma Surg.* **2014**, *134*, 1271–1277. [CrossRef]
47. Yüksel, S.; Adanir, O.; Gultekin, M.Z.; Caglar, A.; Kucukyildirim, B.O.; Alagoz, E.; Gulec, M.A. The examination of the effect of platelet rich plasma for curing achilles tendons of free moving rats after surgical ıncision and treatment. *Acta Orthop. Traumatol. Turc.* **2015**, *49*, 544–551. [CrossRef]
48. Sun, Y.; Kwak, J.-M.; Kholinne, E.; Koh, K.-H.; Tan, J.; Jeon, I.-H. Subacromial bursal preservation can enhance rotator cuff tendon regeneration: A comparative rat supraspinatus tendon defect model study. *J. Shoulder Elb. Surg.* **2021**, *30*, 401–407. [CrossRef]
49. Oztermeli, A.; Karaca, S.; Yucel, I.; Midi, A.; Sen, E.I.; Ozturk, B.Y. The effect of erythropoietin on rat rotator cuff repair model: An experimental study. *J. Orthop. Surg.* **2019**, *27*. [CrossRef]
50. Pecin, M.; Kreszinger, M.; Vukovic, S.; Lipar, M.; Smolec, O.; Radisic, B.; Kos, J. Accelerated Achilles tendon healing with interleukin-1 receptor antagonist protein in rabbits. *Turk. J. Veter. Anim. Sci.* **2017**, *41*, 118–126. [CrossRef]
51. Saha, P.K. Analysis of Results of Platelet-rich Plasma with Arthroscopic Acromioplasty and Arthroscopic Acromioplasty: A Comparative Study. *Int. J. Sci. Stud.* **2016**, *4*, 87–91. [CrossRef]
52. Kokubu, S.; Inaki, R.; Hoshi, K.; Hikita, A. Adipose-derived stem cells improve tendon repair and prevent ectopic ossification in tendinopathy by inhibiting inflammation and inducing neovascularization in the early stage of tendon healing. *Regen. Ther.* **2020**, *14*, 103–110. [CrossRef]
53. Dallaudière, B.; Lempicki, M.; Pesquer, L.; Louedec, L.; Preux, P.M.; Meyer, P.; Hess, A.; Durieux, M.H.M.; Hummel, V.; Larbi, A.; et al. Acceleration of tendon healing using US guided intratendinous injection of bevacizumab: First pre-clinical study on a murine model. *Eur. J. Radiol.* **2013**, *82*, e823–e828. [CrossRef]
54. Hooijmans, C.R.; Rovers, M.M.; De Vries, R.B.M.; Leenaars, M.; Ritskes-Hoitinga, M.; Langendam, M.W. SYRCLE's risk of bias tool for animal studies. *BMC Med. Res. Methodol.* **2014**, *14*, 43. [CrossRef]
55. Higgins, J.P.T.; Altman, D.G.; Gøtzsche, P.C.; Jüni, P.; Moher, D.; Oxman, A.D.; Savović, J.; Schulz, K.F.; Weeks, L.; Sterne, J.A.C.; et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* **2011**, *343*, d5928. [CrossRef]
56. Foster, T.E.; Puskas, B.L.; Mandelbaum, B.R.; Gerhardt, M.B.; Rodeo, S.A. Platelet-Rich Plasma. *Am. J. Sports Med.* **2009**, *37*, 2259–2272. [CrossRef]
57. Connell, D.A.; Ali, K.E.; Ahmad, M.; Lambert, S.; Corbett, S.; Curtis, M. Ultrasound-guided autologous blood injection for tennis elbow. *Skelet. Radiol.* **2006**, *35*, 371–377. [CrossRef]
58. Suresh, S.P.S.; Ali, K.E.; Jones, H.; Connell, D.A.; Beall, D.P.; Klauser, A.S. Medial epicondylitis: Is ultrasound guided autologous blood injection an effective treatment? *Br. J. Sports Med.* **2006**, *40*, 935–939. [CrossRef]
59. De Vos, R.J.; Weir, A.; Van Schie, H.T.M.; Bierma-Zeinstra, S.M.A.; Verhaar, J.A.N.; Weinans, H.; Tol, J.L. Platelet-Rich Plasma Injection for Chronic Achilles Tendinopathy. *JAMA* **2010**, *303*, 144–149. [CrossRef]
60. Docking, S.I.; Cook, J.; Chen, S.; Scarvell, J.; Cormick, W.; Smith, P.; Fearon, A. Identification and differentiation of gluteus medius tendon pathology using ultrasound and magnetic resonance imaging. *Musculoskelet. Sci. Pr.* **2019**, *41*, 1–5. [CrossRef]
61. Okazaki, Y.; Furumatsu, T.; Maehara, A.; Miyazawa, S.; Kamatsuki, Y.; Hino, T.; Ozaki, T. Histological alterations to the hamstring tendon caused by cleaning during autograft preparation. *Muscle Ligaments Tendons J.* **2019**, *9*, 217. [CrossRef]
62. Zabrzynski, J.; Gagat, M.; Paczesny, L.; Grzanka, D.; Huri, G. Correlation between smoking and neovascularization in biceps tendinopathy: A functional preoperative and immunohistochemical study. *Ther. Adv. Chronic Dis.* **2020**, *11*. [CrossRef]
63. De Vos, R.-J.; Weir, A.; Cobben, L.P.J.; Tol, J.L. The Value of Power Doppler Ultrasonography in Achilles Tendinopathy. *Am. J. Sports Med.* **2007**, *35*, 1696–1701. [CrossRef]
64. Alfredson, H.; Öhberg, L. Sclerosing injections to areas of neo-vascularisation reduce pain in chronic Achilles tendinopathy: A double-blind randomised controlled trial. *Knee Surg. Sports Traumatol. Arthrosc.* **2005**, *13*, 338–344. [CrossRef]