

# Autologous growth factor injections in chronic tendinopathy: a systematic review

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Chronic degenerative tendinopathies are frequent and difficult to treat. Tendon healing and regeneration may be improved by injecting autologous growth factors obtained from the patient's blood. Autologous growth factors can be injected with autologous whole blood or platelet-rich plasma (PRP). Electronic databases were searched for prospective clinical trials on treatment with autologous growth factors of patients with chronic tendinopathy. Chronic tendinopathy in this study included wrist extensors, flexors, plantar fasciopathy and patellar tendinopathy. Studies examining the treatment of other tendinopathies were not identified. The Physiotherapy Evidence Database score was used to examine the methodological quality of the assessment, and a qualitative analysis was performed with the levels of evidence. There are many proposed treatment options for chronic tendinopathy. Treatments in the form of injections with autologous whole blood or PRP are increasingly used in clinical practice. There are high expectations of these regenerative injections, and there is a clear need for effective conservative therapies. All studies showed that injections of autologous growth factors (whole blood and PRP) in patients with chronic tendinopathy had a significant impact on improving pain and/or function over time. However, only three studies using autologous whole blood had a high methodological quality assessment, and none of them showed any benefit of an autologous growth factor injection when compared with a control group. At present, there is strong evidence that the use of injections with autologous whole blood should not be recommended. There were no high-quality studies found on PRP treatment. There is limited evidence to support the use of injections with PRP in the management of chronic tendinopathy. There is growing interest in the working mechanisms of autologous growth factors. The amount and mixture of growth factors produced using different cell separating systems are largely unknown and it is also uncertain whether platelet activation prior to injection is necessary. These variables should be taken into account when starting clinical studies. A good experimental model for studying tendinopathy would be helpful for basic research. Future clinical studies using a proper control group, randomization, blinding and validated disease-specific outcome measures for pain and function are needed.

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## Introduction

Chronic painful tendon disorders are common in athletic and sedentary individuals.<sup>1-4</sup> They are more common in middle age, and with increasing in sports participation at increasing ages, they are becoming more frequent.<sup>1,2</sup> The Achilles tendon, patella tendon, wrist extensors, plantar fascia and supraspinatus tendon are commonly affected larger tendons.<sup>5</sup> Multiple aetiological factors probably play a role in the pathogenesis of these conditions.<sup>1-5</sup>

If the triad of pain, swelling and a reduced load bearing capacity are present, then the correct term for the diagnosis is tendinopathy.<sup>1</sup> This is a clinical and not a histopathological diagnosis.<sup>1,3</sup> A failed healing repair process at tissue level results in a variety of histopathological changes, including degeneration, of the tendon tissue.<sup>3</sup> Tendinopathy leads to a reduction in activity levels and sometimes to cessation of all sporting activities.<sup>4</sup>

Increasing knowledge of the pathology and pathogenesis of tendinopathy has led to the introduction of a large number of conservative treatments. At present, the best available evidence points towards the use of heavy load eccentric training programmes.<sup>6</sup> Conventional conservative therapy is ineffective in around 25% of patients with Achilles tendinopathy.<sup>7</sup> In these patients, surgery can be performed, but it is not always successful, and the post-operative rehabilitation is slow and time consuming.<sup>3,4,6-8</sup> To reduce the need for surgery, more effective conservative therapies are needed.

Recently, research has focused on regenerative therapies with high expectations of success.<sup>9,10</sup> The use of autologous growth factors is thought to lead to tendon healing through collagen regeneration and the stimulation of a well-ordered angiogenesis.<sup>9,10</sup> These growth factors are administered in the form of autologous whole blood or platelet-rich plasma (PRP).<sup>9</sup> Platelets can be isolated using simple cell-separating systems.<sup>9,11</sup> The degranulation of the  $\alpha$ -granules in the platelets releases many different growth factors that play a role in tissue regeneration processes. Platelet-derived growth factor, transforming growth factor- $\beta$ , vascular-derived endothelial growth factor, epithelial growth factor, hepatocyte growth factor and insulin-like growth factor are examples of such growth factors.<sup>9-12</sup> Injections with autologous growth factors are becoming common in clinical practice.<sup>10,11</sup>

This systematic review examines the literature on the effects of autologous blood and PRP injections in the management of tendinopathies.

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## Methods

### *Literature search*

A comprehensive, systematic literature search was performed in October 2009. The databases of PubMed, MEDLINE, EMBASE, CINAHL and the Cochrane library were searched without time limits. The following key words were used in differing combinations: 'tendinopathy', 'tendinosis', 'tendinitis', 'tendons', 'tennis elbow', 'plantar fasciitis', 'platelet rich plasma', 'platelet transfusion', 'autologous blood' or 'injection'. The search was limited to articles in English, and only human studies were included. All titles and abstracts were assessed by two researchers, and all relevant articles were obtained. All bibliographies were also hand searched to identify further relevant literature.

All relevant articles were read independently in full text by two researchers to assess whether they met the inclusion criteria. If there was a difference in opinion on suitability, a consensus was reached by consulting a third reviewer.

### *Study selection*

Articles were suitable (inclusion criteria) if the subjects had been clinically diagnosed as having chronic tendinopathy. The design had to be a prospective clinical study; randomized controlled trial (RCT), non-randomized clinical trial (CCT) or prospective case series. There had to be a well-described intervention in the form of an injection with either PRP or autologous blood. The outcome had to be reported in terms of pain and/or function.

### *Data extraction*

Two researchers independently recorded the study design, population, intervention, outcome measure and outcome using standardized data extraction forms.<sup>13</sup> To assess the efficacy of the interventions, mean values of the continuous outcomes were extracted from the published articles.

### *Quality assessment*

The studies included were scored using the PEDro (Physiotherapy Evidence Database) score.<sup>14</sup> The PEDro score is an 11-point list using yes and no answers. The first statement pertains to the external validity

**Table 1** PEDro scale.

Items
1. Eligibility criteria were specified
2. Subjects were randomly allocated to groups
3. Allocation was concealed
4. The groups were similar at baseline regarding the most important prognostic indicators
5. There was blinding of all subjects
6. There was blinding of all therapists who administered the therapy
7. There was blinding of all assessors who measured at least one key outcome
8. Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups
9. All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome were analysed by 'intention to treat'
10. The results of between-group statistical comparisons are reported for at least one key outcome
11. The study provides both point measures and measures of variability for at least one key outcome

The score is the number of positive answers on questions 2–11 (0–10).

of the study and is not used to compute the final quality score. The score (0–10) is the number of positive answers on questions 2–11. The PEDro items are shown in Table 1.

To assess the reliability of consensus ratings using the PEDro scale, a study was conducted by Maher *et al.*<sup>14</sup> A random selection of 120 RCTs was assessed four times by four different raters. Intraclass correlation coefficient for consensus ratings using the PEDro scale showed to be 0.68, which compares to a 'fair' to 'good' reliability.<sup>15</sup> It was suggested that the PEDro scale has sufficient reliability for its use in systematic reviews of physiotherapy trials,<sup>14</sup> and recently it has been used in a systematic review on the effects of exercise treatment in tendinopathy.<sup>16</sup>

A PEDro score of 6 or higher is considered to represent a high-quality study.<sup>16</sup> The results of the quality assessments of the individual trials were used to classify the level of evidence.<sup>17</sup> This qualitative analysis was performed with five levels of evidence based upon the quality and results of clinical studies:

1. strong evidence: provided by generally consistent findings in multiple high-quality RCTs
2. moderate evidence: provided by generally consistent findings in one high-quality RCTs and one or more lower-quality RCTs, or by generally consistent findings in multiple low-quality RCTs
3. limited evidence: provided by only one RCT (either high or low quality) or generally consistent findings in CCTs
4. conflicting evidence: inconsistent findings in multiple RCTs or CCTs
5. no evidence: no RCTs or CCTs

Studies with a high methodological score using the PEDro scale were considered as high-quality studies and those with a low PEDro score were considered low-quality studies.

## Results

### Literature search

Thirteen studies were included after screening. Two studies were excluded (figure 1).<sup>43,44</sup> Eleven studies were suitable for quality assessment and were assessed using the PEDro score.

### Study design

There were six observational non-controlled studies<sup>18–23</sup> and five controlled clinical trials<sup>24–28</sup> of which two were evaluated as having appropriate randomisation.<sup>24,28</sup>

### Participants

The mean number of subjects was 40.5 (SD 24.6) with a range 20–100. Four studies were on patients with chronic tendinopathy of the wrist extensors (tennis elbow)<sup>18,19,23,25</sup> of which one study on both wrist extensor and flexor tendinopathy (golfer's elbow).<sup>25</sup> One study evaluated the treatment effect on tendinopathy of wrist flexors.<sup>20</sup> Patients with chronic plantar fasciopathy were treated in three studies<sup>24,27,28</sup> and three studies had examined patients with chronic patellar tendinopathy.<sup>21,22,26</sup>

### Interventions

There were eight studies on the effects of autologous blood injections,<sup>18–21,23,24,27,28</sup> of which five studies used this in combination with a local anaesthetic<sup>18–21,24</sup> and the other three studies applied only autologous blood.<sup>23,27,28</sup>

There were three studies on PRP injections,<sup>22,25,26</sup> of which one used an additional local anaesthetic<sup>25</sup> and two did not report whether local anaesthesia was used.<sup>22,26</sup> In three studies a single injection,<sup>24,25,27</sup> in one study two injections<sup>21</sup> and in two studies three injections<sup>22,26</sup> were used. In the other five studies, a varying number of injections (1–3) were given.<sup>18–20,23,28</sup> The PRP was prepared using a single<sup>25</sup> or double<sup>22,26</sup> centrifuging process. In two studies, calcium was added to the PRP for activation of the platelets.<sup>22,26</sup>

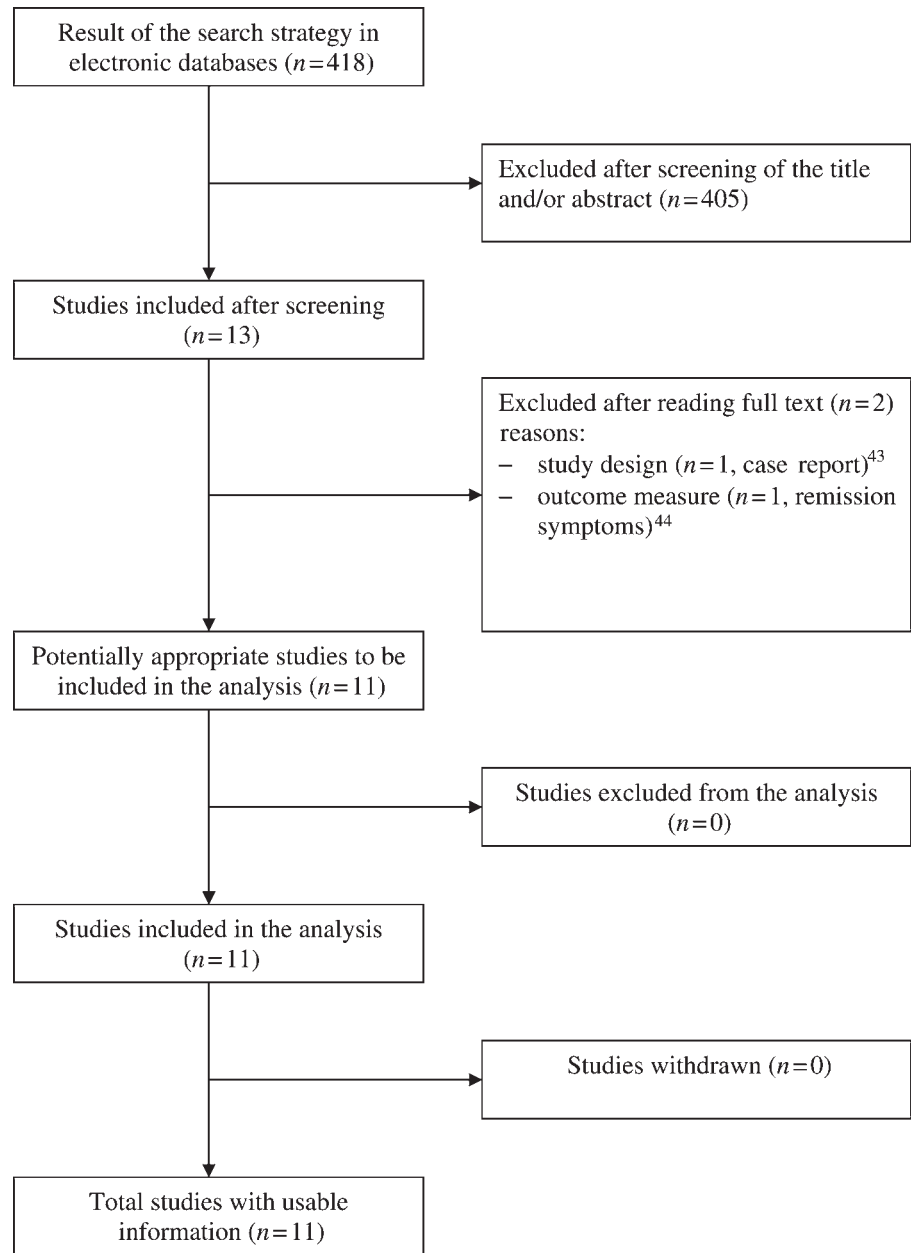


Fig. 1 QUOROM statement flow diagram.

### Outcome measures

Ten of the 11 studies used a visual analogue scale or ordinal scale to measure pain.<sup>18–20,22–28</sup> In four studies, the elbow function was quantified using the Nirschl score.<sup>18–20,23</sup> The Nirschl score runs from 1;

**Table 2** Included studies.

Reference	Number of participants	Study design	Inclusion criteria	Intervention	Control group(s)	Primary outcome measures	Follow-up (months)	Outcome in intervention group (% improvement)	Outcome in control group(s) (% improvement)
Edwards and Calandruccio <sup>18</sup>	28	Case series	Wrist extensor tendinopathy	1–3 autologous blood injection(s)	—	Pain scale (0–10)  Nirschl score (0–7)	9.5	Mean pain score: 7.8 to 2.3 (71%)  Mean Nirschl score: 6.5 to 2.0 (69%)	—
Mishra and Pavelko <sup>25</sup>	20	CCT	Wrist extensor and flexor tendinopathy	1 PRP injection	C: 1 anaesthetic injection	VAS score (0–100)  Modified Mayo elbow score (0–100)	25.6	Mean VAS score: 80.3 to 5.7 (93%) Mean Modified Mayo elbow score: NA	C: Mean VAS score: NA Mean Modified Mayo elbow score: NA
Suresh <i>et al.</i> <sup>20</sup>	20	Case series	Wrist flexor tendinopathy	2–3 autologous blood injections	—	VAS score (0–10)  Nirschl score (0–7)	10	Mean VAS score: 8.0 to 2.2 (73%) Median Nirschl score: 6.0 to 1.0 (83%)	—
Connell <i>et al.</i> <sup>19</sup>	35	Case series	Wrist extensor tendinopathy	2–3 autologous blood injections	—	VAS score (0–10)  Nirschl score (0–7)	6	Median VAS score: 9.0 to 0.0 (100%) Median Nirschl score: 6.0 to 0.0 (100%)	—
Kiter <i>et al.</i> <sup>28</sup>	54	RCT	Plantar fasciopathy	1–3 autologous blood injection(s)	C1: 1–2 corticosteroid injection(s) C2: dry needling	VAS score (0–10)  AOFAS score (0–100)	6	Mean VAS score: 7.6 to 2.4 (68%) Mean AOFAS score: 71.6 to 80.9 (33%)	C1: Mean VAS score: 7.3 to 2.6 (65%) <sup>†</sup> Mean AOFAS score: 65.7 to 80.1 (42%) <sup>†</sup> C2: Mean VAS score: 6.4 to 2.0 (69%) <sup>†</sup> Mean AOFAS score: 64.1 to 78.2 (39%) <sup>†</sup>
Ul Gani <i>et al.</i> <sup>23</sup>	26	Case series	Wrist extensor tendinopathy	1–2 autologous blood injection(s)	—	Pain scale (1–4)	8	Mean pain score: 3.3 to 1.2 (64%)	—

Continued

Table 2 Continued

Reference	Number of participants	Study design	Inclusion criteria	Intervention	Control group(s)	Primary outcome measures	Follow-up (months)	Outcome in intervention group (% improvement)	Outcome in control group(s) (% improvement)
James <i>et al.</i> <sup>21</sup>	47	Case series	Patellar tendinopathy	2 autologous blood injections combined with dry needling	—	Nirschl score (0–7) VISA-P score (0–100)	14.8	Mean Nirschl score: 5.5 to 2.1 (62%) Mean VISA-P score: 39.8 to 74.3 (57%)	—
Lee and Ahmad <sup>24</sup>	64	RCT	Plantar fasciopathy	1 autologous blood injection	C: 1 corticosteroid injection	VAS score (0–10)	6	Mean VAS score: 7.3 to 3.6 (51%)	C: Mean VAS score: 6.9 to 2.4 (65%) <sup>†</sup>
Kon <i>et al.</i> <sup>22</sup>	20	Case series	Patellar tendinopathy	3 PRP injections	—	EQ-VAS score (0–100) Tegner score (0–10)	6	Mean EQ-VAS score: 57 to 82 (58%) Mean Tegner score: 4 to 7 (50%)	—
Filardo <i>et al.</i> <sup>26</sup>	31	CCT	Patellar tendinopathy	3 PRP injections	C: exercise therapy	EQ-VAS score (0–100) Tegner score (0–10)	6	Mean EQ-VAS score: 52.7 to 78.3 (54%) Mean Tegner score: 3.7 to 6.6 (46%)	C: Mean EQ-VAS score: 50.6 to 73.5 (46%) <sup>†</sup> Mean Tegner score: 5.3 to 6.8 (32%)*
Kalaci <i>et al.</i> <sup>27</sup>	100	CCT	Plantar fasciopathy	1 autologous blood injection	C1: 1 corticosteroid injection C2: 1 corticosteroid injection combined with dry needling C3: 1 anaesthetic injection combined with dry needling	VAS score (0–10)	6	Mean VAS score: 6.8 to 3.5 (48%)	C1: Mean VAS score: 7.0 to 1.5 (78%) <sup>†</sup> C2: Mean VAS score: 7.2 to 1.0 (87%) <sup>†</sup> C3: Mean VAS score: 6.7 to 3.4 (48%) <sup>†</sup>

Improvements were calculated after correcting for scale and baseline score. CCT, non-randomized clinical trial; RCT, randomized controlled trial; VAS, visual analogue scale; VISA-P, Victorian Institute of Sports Assessment-Patella; AOFAS, American Orthopaedics Foot and Ankle (rearfoot score); NA, not available; C, control group. \*Significant improvement in favour of autologous growth factor injection. <sup>†</sup>No significant difference with control group. <sup>‡</sup>Significant improvement in favour of control group.



mild pain during activity to 7; constant pain at rest. To our knowledge, there are no data available on the validity of the Nirschl score. One study<sup>21</sup> used the Victorian Institute of Sports Assessment-Patella (VISA-P) score which is a validated outcome measure for patellar tendinopathy that assesses pain and function. It runs from 0 representing maximal pain and minimal function to 100 which represents no pain and maximal functioning. The two other studies on patellar tendinopathy used the Tegner score to quantify activity level.<sup>22,26</sup> The Tegner score runs from 0 to 10 with 0 being invalidated and 10 representing specific professional sports activities. The Tegner score previously showed an acceptable validity in the evaluation of meniscal injuries.<sup>29</sup> One study on plantar fasciopathy used the rearfoot score of the American Orthopaedics Foot and Ankle (AOFAS) to assess function.<sup>28</sup> There are no data available on the validity of the AOFAS score for the evaluation of plantar fasciopathy. This score runs from 0 to 100; a score of 100 represents no pain and optimal functioning. One study used the modified Mayo elbow score, which was not recorded at final follow-up.<sup>25</sup>

## Outcomes

All the intervention groups reported a significant improvement in the pain and/or function scores with the mean improvement being 66% (SD 19, range 33–100). The outcomes in the control groups also improved significantly in all the studies with a mean improvement of 57% (SD 18, range 32–87). These improvements were reported after a mean follow-up of 9.4 months (SD 6.0). There was in none of the included studies a beneficial effect on pain score at final follow-up after autologous growth factor injections when compared with a control group.<sup>24,26–28</sup> One study reported a significant improvement on the functional Tegner score when compared with the control group, but the statistical baseline difference in Tegner score between these groups was not reported.<sup>26</sup> In four other control groups, there were similar results on pain and/or function when compared with autologous growth factor injections.<sup>24,27,28</sup> In two control groups, there was a significant improvement on pain in favour of the control group.<sup>27</sup> Table 2 gives an overview of these differences.

## Sample-size calculation

Only one trial reported a sample-size calculation.<sup>22</sup> Kon *et al.* reported that 20 cases were needed to detect a clinically important increase of

**Table 3** Particular scoring of the included studies for methodological quality according to the PEDro score.

Reference	Item PEDro score											Total score
	1	2	3	4	5	6	7	8	9	10	11	
Edwards and Calandruccio <sup>18</sup>	+	-	-	-	-	-	-	+	+	-	-	2/10
Mishra and Pavelko <sup>25</sup>	+	-	-	-	-	-	-	-	-	+	+	2/10
Suresh et al. <sup>20</sup>	+	-	-	-	-	-	-	-	-	-	+	1/10
Connell et al. <sup>19</sup>	+	-	-	-	-	-	-	-	-	-	+	1/10
Kiter et al. <sup>28</sup>	+	+	-	+	-	-	+	+	+	+	+	7/10
Ul Gani et al. <sup>23</sup>	+	-	-	-	-	-	-	+	+	-	-	2/10
James et al. <sup>21</sup>	+	-	-	-	-	-	-	+	-	-	+	2/10
Lee and Ahmad <sup>24</sup>	+	+	-	+	-	-	+	+	+	+	+	7/10
Kon et al. <sup>22</sup>	+	-	-	-	-	-	-	+	+	-	+	3/10
Filardo et al. <sup>26</sup>	+	-	-	-	-	-	-	+	+	+	+	4/10
Kalaci et al. <sup>27</sup>	+	-	-	-	+	-	+	+	+	+	+	6/10

The total score was defined by the number of positive answers on questions 2–11 (0–10).

15 points on the VAS score. All other included studies did not report using a sample-size calculation.

### Methodological quality

The PEDro scores for the 11 studies are shown in Table 3. The scores ranged from 1 to 7 with an average of 3.4 (SD 2.3). Three studies were considered as being high quality (PEDro score  $\geq 6$ ) and the other eight studies were of low quality (PEDro score  $< 6$ ). All the studies reported the inclusion criteria. A comparison to another treatment was performed in five studies, and randomization was used in two studies. Blinding of the treatment was undertaken for patients in one study,<sup>27</sup> for the treating physician in none of the studies and for the outcome assessor in three studies.<sup>24,27,28</sup> In three studies, more than 15% of the patients were lost to follow-up,<sup>19,20,25</sup> and in four studies, the data analysis was not performed on an ‘intention to treat’ basis.<sup>19–21,25</sup> Two studies had poor reporting of the statistical analysis.<sup>18,23</sup>

### Level of evidence

Until now, three high-quality studies<sup>24,27,28</sup> on the use of autologous growth factor injections (all used autologous blood injections) for the management of chronic tendinopathy showed no significant improvement when compared with a control group. One study showed a significantly superior improvement after a corticosteroid injection in comparison with one single autologous blood injection.<sup>27</sup> Two of these

high-quality studies were RCTs. As such, there is level 1 (strong) evidence of no improvement in pain and/or function in chronic tendinopathy after injecting autologous blood when compared with other treatment options. If PRP injections were to be considered separately, three low-quality studies were included, and so there is level 3 (limited) evidence that these injections improve pain and/or function in chronic tendinopathy.

## Discussion

A total of 11 articles were suitable for inclusion in this systematic review on the use of autologous growth factors in the treatment of chronic tendinopathy. Three studies, of which two were RCTs, were of high quality. All studies showed an improvement in pain and function scores, but there was no difference when compared with the improvement in pain scores in the control groups. After a qualitative analysis, there was level one (strong) evidence that injections with autologous blood were not of benefit. Currently, there is level 3 (limited) evidence that PRP injections improve pain and/or function in chronic tendinopathy.

These findings are clinically relevant, as the use of autologous growth factors is gaining popularity.<sup>9–11</sup> This results in part from laboratory studies showing positive and promising results.<sup>30–32</sup> Autologous growth factors have the potential to change collagen production and degradation by influencing matrix regulating enzymes.<sup>9,10,33</sup> Laboratory studies showed that the addition of PRP to human tenocytes resulted in cell proliferation, collagen deposition and improved gene expression for matrix degrading enzymes and endogenous growth factors.<sup>30</sup> A recent animal study found similar results,<sup>31</sup> and the *in vivo* application of PRP suggested an accelerated remodelling and angiogenic process. Bosch *et al.*<sup>32</sup> performed a placebo-controlled ultrasound study on the recovery of horse tendons using PRP which showed an increase in anti-inflammatory response and fibrillogenesis in the short term. At longer-term follow-up, an increased, collagen matrix integrity was found in the PRP treated tendons.

Although the results of laboratory studies are encouraging, they always use healthy tendons or surgically induced lesions given the lack of a good experimental model for tendinopathy. At present, it is unclear whether these results can be extrapolated to tendinopathic tendons, and future research in the field of basic science should study this.

This systematic review makes it clear that there is a lack of good quality studies in this field, especially regarding treatment with PRP. The commonest methodological flaws are the lack of a suitable control

group, randomization and blinding of subjects and those involved in the treatment. One research group reported that the study design was a RCT,<sup>27</sup> but after critically reading the full-text, it became apparent that this study was a CCT. Another research group selected a very small control group of five patients and reported a significant improvement in pain and function scores in the PRP group compared with this small control group after 8 weeks.<sup>25</sup> However, the patients in the control group were lost to follow-up already after 8 weeks and could not be included in the final analysis. Although there was a consensus that this was a CCT, the authors agreed that the control group was not appropriate. Although these methodological processes are relatively simple to implement, it does make the research process more intensive and less attractive for potential subjects. It is not uncommon for pilot studies to be performed to assess the effect size of new treatments before progressing to evaluate their use in randomized controlled clinical trials. Lower-quality studies on the management of tendinopathy evidence better results than good-quality studies.<sup>34</sup> Future studies should therefore use appropriate randomization, and all those involved should be blinded to the treatment given.

A few other suggestions on future research can also be made. There may be differences in natural healing response between load-bearing tendons, such as the patellar and Achilles tendon, and non-load-bearing tendons, such as the wrist extensors and flexors. Wrist extensor tendinopathy is a self-limiting disease with 80–90% recovery within 1 year,<sup>35</sup> whereas patients with tendinopathy of the main body of the Achilles tendon did not improve in a trial with a four month wait and see arm.<sup>36</sup> In some studies, the subjects included had a variety of mid-portion and insertional tendinopathies, and it is unclear whether these can be compared, as these portions of the tendon have differing biomechanical and metabolic properties and responses to treatment.<sup>5</sup> This makes comparing the results of studies on differing locations of tendinopathy difficult and emphasizes the need of suitable control groups.

Many of the studies on the effect of injections with autologous growth factors used a mixture with local anaesthetic which could lead to bias, as an injection with local anaesthetic alone led to improvement in a previous trial on elbow tendinopathy.<sup>35</sup>

Most of the studies included in this review used pain as the primary outcome to assess treatment effect. Only one study had used the VISA-P score, a validated outcome questionnaire for patellar tendinopathy. Four studies used the Nirschl score, which does give a global impression of pain in combination with activity. Outcome assessment should focus on activity as well as pain when studying tendinopathy and where possible use disease-specific validated measures.<sup>37</sup> Another important feature of outcome assessment is the prior establishment of

the minimally important clinical difference. Only one study of those included reported a sample size calculation with the use of a clinically relevant difference.<sup>22</sup> In osteoarthritis research, minimally important clinical differences are defined for different outcome measures,<sup>38</sup> but these values are lacking in tendinopathy research.

No studies to date have compared an injection with autologous growth factors to a placebo injection. The effects of placebo treatments are greater the more invasive they are,<sup>39</sup> and a recent tendinopathy study showed a large effect after a placebo injection was performed.<sup>40</sup> Currently, there have also been no studies that have compared autologous blood to PRP. This would be interesting given the larger costs and practical difficulties associated with preparing PRP.

Along with treatment effects it is also necessary to report and monitor for complications.<sup>33</sup> In the studies included here, no complications were reported but it is important to monitor for infections, ruptures and possible systemic effects when using autologous growth factors.

There are still many unanswered questions in this field. There has been little research performed on the amount of growth factors produced using different cell separating systems, and what the optimal mixture would be.<sup>10,11</sup> It is unclear what the best volume and frequency of the injections is. Moreover, when multiple injections are considered, the ideal period between multiple injections is unknown. It is also uncertain whether platelet activation prior to injection is necessary, as contact with collagen would also lead to platelet degranulation.<sup>41,42</sup>

## Conclusion

There is strong evidence that autologous blood injections do not improve pain and/or function compared with other treatment options. There is only limited evidence that PRP injections are beneficial. All three high-quality studies on the use of autologous growth factor injections in the management of chronic tendinopathy showed no benefit. All studies did show an effect on pain and function in time, but many are seriously methodologically flawed. To date, there is strong evidence that the use of injections with autologous blood should not be recommended, and there is limited evidence to support the use of injections with PRP in the treatment of chronic tendinopathy. Further studies using a proper control group, randomization, blinding and validated disease-specific outcome measures for pain and function are needed.

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