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.
Keywords: tendinopathy/tendon/autologous growth factors/autologous blood/platelet-rich plasma/injection therapy

Introduction

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

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

Increasing knowledge of the pathology and pathogenesis of tendinopathy has lead 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.⁶ Conventional conservative therapy is ineffective in around 25% of patients with Achilles tendinopathy.⁷ In these patients, surgery can be performed, but it is not always successful, and the post-operative rehabilitation is slow and time consuming.³,⁴,⁶–⁸ To reduce the need for surgery, more effective conservative therapies are needed.

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

This systematic review examines the literature on the effects of autologous blood and PRP injections in the management of tendinopathies.
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. 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. The PEDro score is an 11-point list using yes and no answers. The first statement pertains to the external validity...
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. 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. It was suggested that the PEDro scale has sufficient reliability for its use in systematic reviews of physiotherapy trials, and recently it has been used in a systematic review on the effects of exercise treatment in tendinopathy.

A PEDro score of 6 or higher is considered to represent a high-quality study. The results of the quality assessments of the individual trials were used to classify the level of evidence. 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 RCT 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

Table 1 PEDro scale.

<table>
<thead>
<tr>
<th>Items</th>
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<tbody>
<tr>
<td>1. Eligibility criteria were specified</td>
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<tr>
<td>2. Subjects were randomly allocated to groups</td>
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<tr>
<td>3. Allocation was concealed</td>
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<td>4. The groups were similar at baseline regarding the most important prognostic indicators</td>
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<tr>
<td>5. There was blinding of all subjects</td>
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<tr>
<td>6. There was blinding of all therapists who administered the therapy</td>
</tr>
<tr>
<td>7. There was blinding of all assessors who measured at least one key outcome</td>
</tr>
<tr>
<td>8. Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups</td>
</tr>
<tr>
<td>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’</td>
</tr>
<tr>
<td>10. The results of between-group statistical comparisons are reported for at least one key outcome</td>
</tr>
<tr>
<td>11. The study provides both point measures and measures of variability for at least one key outcome</td>
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</table>

The score is the number of positive answers on questions 2–11 (0–10).
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).\(^43,44\) Eleven studies were suitable for quality assessment and were assessed using the PEDro score.

**Study design**

There were six observational non-controlled studies\(^18–23\) and five controlled clinical trials\(^24–28\) of which two were evaluated as having appropriate randomisation.\(^24,28\)

**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)\(^18,19,23,25\) of which one study on both wrist extensor and flexor tendinopathy (golfer’s elbow).\(^25\) One study evaluated the treatment effect on tendinopathy of wrist flexors.\(^20\) Patients with chronic plantar fasciopathy were treated in three studies\(^24,27,28\) and three studies had examined patients with chronic patellar tendinopathy.\(^21,22,26\)

**Interventions**

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

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

Ten of the 11 studies used a visual analogue scale or ordinal scale to measure pain.\textsuperscript{18–20,22–28} In four studies, the elbow function was quantified using the Nirschl score.\textsuperscript{18–20,23} The Nirschl score runs from 1;
<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of participants</th>
<th>Study design</th>
<th>Inclusion criteria</th>
<th>Intervention</th>
<th>Control group(s)</th>
<th>Primary outcome measures</th>
<th>Follow-up (months)</th>
<th>Outcome in intervention group (% improvement)</th>
<th>Outcome in control group(s) (% improvement)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edwards and Calandruccio</td>
<td>28</td>
<td>Case series</td>
<td>Wrist extensor</td>
<td>1–3 autologous blood injection(s)</td>
<td>—</td>
<td>Pain scale (0–10)</td>
<td>9.5</td>
<td>Mean pain score: 7.8 to 2.3 (71%)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>tendinopathy</td>
<td></td>
<td></td>
<td>Nirschl score (0–7)</td>
<td></td>
<td>Mean Nirschl score: 6.5 to 2.0 (69%)</td>
<td>—</td>
</tr>
<tr>
<td>Mishra and Pavelko</td>
<td>20</td>
<td>CCT</td>
<td>Wrist extensor</td>
<td>1 PRP injection</td>
<td>C: 1 anaesthetic injection</td>
<td>VAS score (0–100)</td>
<td>25.6</td>
<td>Mean VAS score: 80.3 to 5.7 (93%)</td>
<td>C: Mean VAS score: NA</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>and flexor</td>
<td></td>
<td></td>
<td>Modified Mayo elbow score (0–100)</td>
<td></td>
<td>Mean Modified Mayo elbow score: NA</td>
<td>Mean Modified Mayo elbow score: NA</td>
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<tr>
<td>Suresh et al.</td>
<td>20</td>
<td>Case series</td>
<td>Wrist flexor</td>
<td>2–3 autologous blood injections</td>
<td>—</td>
<td>VAS score (0–10)</td>
<td>10</td>
<td>Mean VAS score: 8.0 to 2.2 (73%)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>tendinopathy</td>
<td></td>
<td></td>
<td>Nirschl score (0–7)</td>
<td></td>
<td>Median Nirschl score: 6.0 to 1.0 (83%)</td>
<td>—</td>
</tr>
<tr>
<td>Connell et al.</td>
<td>35</td>
<td>Case series</td>
<td>Wrist extensor</td>
<td>2–3 autologous blood injections</td>
<td>—</td>
<td>VAS score (0–10)</td>
<td>6</td>
<td>Median VAS score: 9.0 to 0.0 (100%)</td>
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<tr>
<td></td>
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<td></td>
<td>tendinopathy</td>
<td></td>
<td></td>
<td>Nirschl score (0–7)</td>
<td></td>
<td>Median Nirschl score: 6.0 to 0.0 (100%)</td>
<td>—</td>
</tr>
<tr>
<td>Kiter et al.</td>
<td>54</td>
<td>RCT</td>
<td>Plantar fasciopathy</td>
<td>1–3 autologous blood injection(s)</td>
<td>C1: 1–2 corticosteroid injection(s)</td>
<td>VAS score (0–10)</td>
<td>6</td>
<td>Mean VAS score: 7.6 to 2.4 (68%)</td>
<td>C1: Mean VAS score: 7.3 to 2.6 (65%)</td>
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<td></td>
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<td></td>
<td>C2: dry needling</td>
<td>AOFAS score (0–100)</td>
<td></td>
<td>Mean AOFAS score: 71.6 to 80.9 (33%)</td>
<td>Mean AOFAS score: 65.7 to 80.1 (42%)</td>
</tr>
<tr>
<td>Ul Gani et al.</td>
<td>26</td>
<td>Case series</td>
<td>Wrist extensor</td>
<td>1–2 autologous blood injection(s)</td>
<td>—</td>
<td>Pain scale (1–4)</td>
<td>8</td>
<td>Mean pain score: 3.3 to 1.2 (64%)</td>
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</tbody>
</table>

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Table 2 Continued

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of participants</th>
<th>Study design</th>
<th>Inclusion criteria</th>
<th>Intervention</th>
<th>Control group(s)</th>
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<th>Follow-up (months)</th>
<th>Outcome in intervention group (% improvement)</th>
<th>Outcome in control group(s) (% improvement)</th>
</tr>
</thead>
<tbody>
<tr>
<td>James et al.21</td>
<td>47</td>
<td>Case series</td>
<td>Patellar tendinopathy</td>
<td>2 autologous blood injections combined with dry needling</td>
<td>—</td>
<td>Nirschl score (0–7)</td>
<td>14.8</td>
<td>Mean Nirschl score: 5.5 to 2.1 (62%)</td>
<td>Mean VISA-P score: 39.8 to 74.3 (57%)</td>
</tr>
<tr>
<td>Lee and Ahmad24</td>
<td>64</td>
<td>RCT</td>
<td>Plantar fasciopathy</td>
<td>1 autologous blood injection</td>
<td>C: 1 corticosteroid injection</td>
<td>VAS score (0–10)</td>
<td>6</td>
<td>Mean VAS score: 7.3 to 3.6 (51%)</td>
<td>C: Mean VAS score: 6.9 to 2.4 (65%)†</td>
</tr>
<tr>
<td>Kon et al.22</td>
<td>20</td>
<td>Case series</td>
<td>Patellar tendinopathy</td>
<td>3 PRP injections</td>
<td>—</td>
<td>EQ-VAS score (0–100)</td>
<td>6</td>
<td>Mean EQ-VAS score: 57 to 82 (58%)</td>
<td>Mean Tegner score: 4 to 7 (50%)</td>
</tr>
<tr>
<td>Filardo et al.26</td>
<td>31</td>
<td>CCT</td>
<td>Patellar tendinopathy</td>
<td>3 PRP injections</td>
<td>C: exercise therapy</td>
<td>EQ-VAS score (0–100)</td>
<td>6</td>
<td>Mean EQ-VAS score: 52.7 to 78.3 (54%)</td>
<td>C: Mean EQ-VAS score: 50.6 to 73.5 (46%)†</td>
</tr>
<tr>
<td>Kalaci et al.27</td>
<td>100</td>
<td>CCT</td>
<td>Plantar fasciopathy</td>
<td>1 autologous blood injection</td>
<td>C1: 1 corticosteroid injection</td>
<td>VAS score (0–10)</td>
<td>6</td>
<td>Mean VAS score: 6.8 to 3.5 (48%)</td>
<td>C1: Mean VAS score: 7.0 to 1.5 (78%)†</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>C2: 1 corticosteroid injection combined with dry needling</td>
<td>C2: 1 corticosteroid injection combined with dry needling</td>
<td>Tegner score (0–10)</td>
<td></td>
<td>C2: Mean VAS score: 7.2 to 1.0 (87%)†</td>
<td>C3: Mean VAS score: 6.7 to 3.4 (48%)†</td>
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<td></td>
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<td></td>
<td></td>
<td>C3: 1 anaesthetic injection combined with dry needling</td>
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</table>

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. †No significant difference with control group. ‡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\(^21\) 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.\(^22,26\) 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.\(^29\) One study on plantar fasciopathy used the rearfoot score of the American Orthopaedics Foot and Ankle (AOFAS) to assess function.\(^28\) 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.\(^25\)

**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.\(^24,26–28\) 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.\(^26\) In four other control groups, there were similar results on pain and/or function when compared with autologous growth factor injections.\(^24,27,28\) In two control groups, there was a significant improvement on pain in favour of the control group.\(^27\) Table 2 gives an overview of these differences.

**Sample-size calculation**

Only one trial reported a sample-size calculation.\(^22\) Kon *et al.* reported that 20 cases were needed to detect a clinically important increase of
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 ≥ 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, for the treating physician in none of the studies and for the outcome assessor in three studies. In three studies, more than 15% of the patients were lost to follow-up, and in four studies, the data analysis was not performed on an ‘intention to treat’ basis. Two studies had poor reporting of the statistical analysis.

**Level of evidence**

Until now, three high-quality studies 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. 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.\(^9\text{–}^\text{11}\) This results in part from laboratory studies showing positive and promising results.\(^30\text{–}^\text{32}\) Autologous growth factors have the potential to change collagen production and degradation by influencing matrix regulating enzymes.\(^9\text{,}^\text{10}\text{,}^\text{33}\) 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.\(^30\) A recent animal study found similar results,\(^31\) and the *in vivo* application of PRP suggested an accelerated remodelling and angiogenic process. Bosch *et al.*\(^32\) 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,27 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.25 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 appro-
priate. 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 progres-
sing to evaluate their use in randomized controlled clinical trials.
Lower-quality studies on the management of tendinopathy evidence
better results than good-quality studies.34 Future studies should there-
fore 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 tendi-
nopathy is a self-limiting disease with 80–90% recovery within 1
year,35 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.36 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 biome-
chanical and metabolic properties and responses to treatment.5 This
makes comparing the results of studies on differing locations of tendi-
nopathy 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.35

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 tendino-
pathy. 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.37 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.\(^\text{22}\) In osteoarthritis research, minimally important clinical differences are defined for different outcome measures,\(^\text{38}\) 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,\(^\text{39}\) and a recent tendinopathy study showed a large effect after a placebo injection was performed.\(^\text{40}\) 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.\(^\text{33}\) 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.\(^\text{10,11}\) 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.\(^\text{41,42}\)

**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.
References


