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ANKLE

Plasma rich in growth factors (PRGF) as a treatment for high ankle sprain in elite athletes: a randomized control trial

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Abstract

Purpose Syndesmotic sprains are uncommon injuries that require prolonged recovery. The influence of ultrasound-guided injections of platelet-rich plasma (PRP) into the injured antero-inferior tibio-fibular ligaments (AITFL) in athletes on return to play (RTP) and dynamic stability was studied.

Methods Sixteen elite athletes with AITFL tears were randomized to a treatment group receiving injections of PRP or to a control group. All patients followed an identical rehabilitation protocol and RTP criteria. Patients were prospectively evaluated for clinical ability to return to full activity and residual pain. Dynamic ultrasound examinations were performed at initial examination and at 6 weeks post-injury to demonstrate re-stabilization of the syndesmosis joint and correlation with subjective outcome.

Results All patients presented with a tear to the AITFL with dynamic syndesmosis instability in dorsiflexion–external rotation, and larger neutral tibia–fibula distance on ultrasound. Early diagnosis and treatment lead to shorter RTP, with 40.8 (±8.9) and 59.6 (±12.0) days for the PRP and control groups, respectively ($p = 0.006$). Significantly less residual pain upon return to activity was found in the PRP group; five patients (62.5 %) in the control group returned to play with minor discomfort versus one patient in the treatment group (12.5 %). One patient in the control group had continuous pain and disability and subsequently underwent syndesmosis reconstruction.

Conclusions Athletes suffering from high ankle sprains benefit from ultrasound-guided PRP injections with a shorter RTP, re-stabilization of the syndesmosis joint and less long-term residual pain.

Level of evidence II.

Keywords Syndesmosis · Injections · Platelet-rich plasma · Ultrasound · Return to play

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Introduction

Injuries of the syndesmotic ligaments, termed high ankle sprains are uncommon, comprising 1–24.6 % of all ankle sprains, [8, 23, 24] with an incidence of 2.4 per 1,000 athlete exposures [24]. They present a diagnostic and therapeutic challenge for the sports physician and can result in prolonged morbidity. There is a paucity of literature on these injuries. The diagnosis and description are not standardized, and the severity of injuries and time lost from sport are poorly documented. Typical recovery time is almost twice as long as that of a severe lateral ankle sprain, [23] with a mean time to return to play (RTP) of 45 days [56]. Residual chronic pain is also more common than following an isolated lateral ankle sprain [27, 41].

The antero-inferior tibio-fibular ligament (AITFL) may be partially torn or completely torn resulting in diastasis of the fibula and tibia. The majority of syndesmotic injuries are incomplete and result in AITFL strain or a partial tear. Isolated AITFL is rare, and complete distal syndesmotic rupture is likely combined with injury to the anterior deltoid and/or the posterior tibio-fibular ligament. A commonly used grading method may also be applied to AITFL injuries and describes the injury as strain (grade 1), partial tear (grade 2), or complete rupture (grade 3) [12].

Platelet-rich plasma (PRP) is being increasingly used to promote musculoskeletal healing by the stimulation of angiogenesis, chemotaxis, and cell proliferation [47]. PRP has been shown to promote recovery in cases of tendinous and ligamentous injury and muscular strain [19, 22, 29, 34, 42] and has been used to shorten recovery and RTP duration [11, 21]. PRP products are prepared from autogenous blood and administration by injection of a volume of PRP preparation or through direct gel application during surgery [47]. Preparation rich in growth factors (PRGF) is a form of PRP, shown to promote the healing of soft tissue injuries, cartilage and bony defects [32, 47].

Ultrasound is an efficient and accurate radiological modality used to diagnose syndesmotic injuries [30, 31]. It has advantages over other imaging modalities including portability, availability, the absence of radiation, and reduced cost [35, 39]. The effect of ultrasound-guided PRP therapeutic injections on recovery, RTP, and dynamic stability following a grade 3 injury of the AITFL was studied in a group of elite athletes. The hypothesis was that the use of PRP would reduce the time needed for injured athletes to RTP, and that they would have reduced pain compared to a control group upon their return.

Materials and methods

From 2007 to 2010, all elite athletes treated at our facility for syndesmosis injuries were invited to participate in the study. A total of 15 eligible patients with 16 high ankle sprain injuries (16 ankles; all grade 3 high ankle sprain, with complete AITFL tears) were enrolled (Fig. 1). Inclusion criteria were the presence of a high ankle sprain with pain and tenderness over the AITFL verified by a positive squeeze test reproducing pain over the AITFL and widening of the syndesmosis on ultrasound during axial loading and external rotation (ER) [31] (Fig. 2) according to the criteria of Mei-Dan et al. [30], CT and MRI. Mean widening of the healthy tibio-fibular clear space was determined by ultrasound as 0.3 mm for ER–neutral (ER–N) and 0.4 mm for ER–internal rotation (ER–IR). Exclusion criteria were the presence of gross syndesmotic instability presenting as frank diastasis on plain radiographs, previous surgery on the syndesmosis, or any pre-existing symptoms of ankle instability.

Patients were randomized to receive either PRP injection therapy or to a control group (Fig. 1). Randomization was performed according to a block randomization method with a block size of two and an allocation ratio of 1:1. The first patient in the study and the first patient in every block were randomized to one of the two study arms. The next diagnosed patient in the block was automatically allocated to the other study arm.

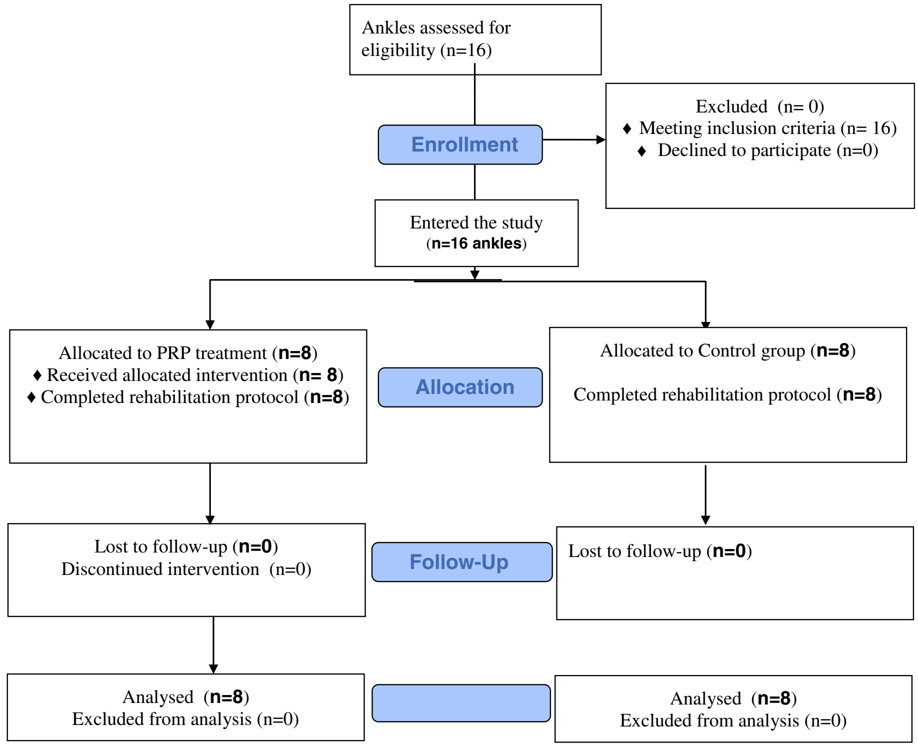
The treatment group received two injections, one at the initial presentation and the second 7 days later, followed by a rehabilitation programme. The control group received the rehabilitation programme.

The distribution of sports participated in was as follows: 11 soccer players, one rugby player, one basketball player, two judokas, and one downhill mountain biker. Treatment and control groups were comparable for age and gender. The gender distribution was 14 males and 2 females (1 female in each group, both judokas). One patient had sustained two high ankle sprain injuries to two different ankles, 1 year apart; randomization assigned him to each treatment group.

PRP preparation and injection technique

A total of 20 ml of peripheral blood was drawn from each patient into four 5 ml trisodium citrate tubes, and a PRGF concentrate was prepared using a validated method resulting in a 2×–3× fold increase in platelet concentration without leucocytes [46]. Tubes were centrifuged with a single spin, at 460 g for 8 min. Under laminar airflow, the plasma fraction located just above the buffy coat (1.5 mL) was aspirated from each tube and dispensed into an empty

Fig. 1 Study flow chart



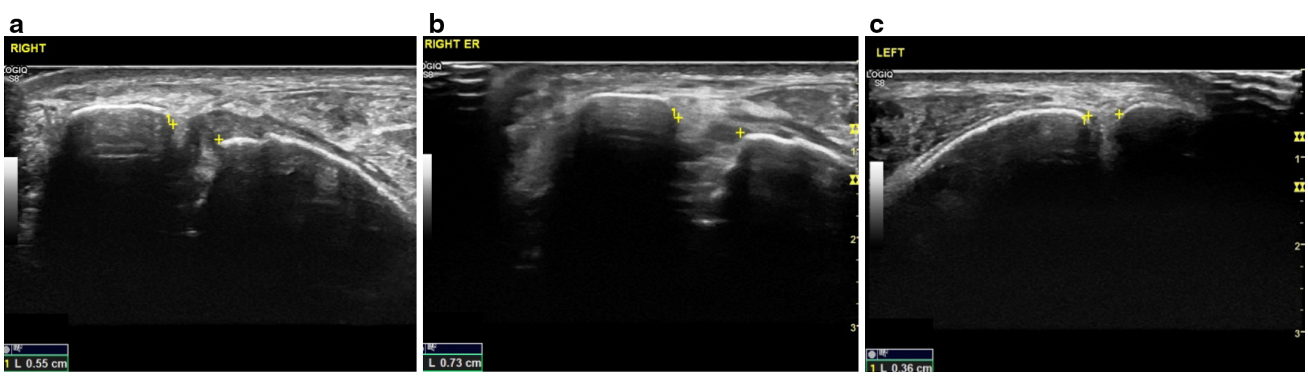


Fig. 2 Sonographic images of an AITFL injury in a professional soccer player, illustrating the widening of the distal tibio-fibular clear space in the neutral (**a**) and external rotation (**b**) positions in the injured ankle and compared to the contralateral ankle (**c**)

tube. Prior to injection, 22.8 mM of calcium chloride was added to the solution. The activated concentrate was then injected before coagulation into the AITFL and distal tibio-fibular joint using a 21-gauge needle under ultrasound guidance so that the fibrin scaffold containing the platelet aggregates would directly form within the region of the AITFL [45, 46].

Ultrasound was used to place the needle deep within the syndesmosis, at the level of the torn AITFL. The PRGF was injected as the needle was gradually withdrawn towards the skin, infiltrating the torn ligament. No local anaesthetic was used for the injections preventing any inhibitory interaction of the anaesthetic and PRGF [33]. The first injection was performed at the time of diagnosis and the second injection 7 days later. All ultrasound examination was performed by an experienced musculoskeletal radiologist using a 6–15-MHz linear transducer LOGIQ 8 GE (General Electric, Fairfield, Connecticut).

Rehabilitation protocol and follow-up

Both groups followed the same rehabilitation protocol and were evaluated with the same RTP criteria. Following the first injection or after the initial diagnosis for control arm, all patients were immobilized in a walking boot in 10° plantar flexion and were mobilized non-weight bearing for the first 11 days. The ankle position was dorsiflexed to

Table 1 Mean (SD) demographics by treatment group

Variable	PRP	Control	Total	p
Mean age in years (SD)	22.6 (4.2) years	22.0 (4.8) y	22.3 (4.4) y	n.s
Side (count)	$R = 5$, $L = 3$	$R = 3$, $L = 5$	$R = 8$, $L = 8$	
Mean RTP in days (SD)	40.8 (8.9)	59.6 (12.0)	49.5 (14.0)	0.006
Residual pain (n %)	1/8 (12.5 %)	5/8 (62.5 %)	6/16 (37.5 %)	
Median Tegner Activity Level (range)	9 (range 7–10)	9 (range 7–10)	9 (range 7–10)	n.s

RTP return to play

neutral after 3–4 days. Progressive weight bearing was permitted from days 11–13. After 2 weeks, unrestricted weight bearing was permitted. All patients then followed the same physical therapy protocol of range of movement exercises, proprioception, peroneal strengthening, and functional rehabilitation. Patients were instructed to avoid dorsiflexion activities for 3 weeks from the time of injury and specifically to avoid landing on a bent knee and ankle joint, as well as cutting/pivoting movements.

Clinical evaluations were performed at 3 weeks post-injury: palpation for tenderness and the calf compression test (squeeze test) [23]. Patients who had no tenderness were pain-free with weight bearing underwent Cotton and dorsiflexion–ER tests [41] accompanied by dynamic ultrasound to assess AITFL healing. Dynamic ultrasound examination looking specifically for syndesmotic stability was performed in all patients at 6 weeks from injury.

Before the athletes were permitted to fully train, they were required to have attained the following functional goals: (1) complete a single-leg jump of at least one metre, landing with a bent knee and deep ankle flexion; (2) complete the CODS (change of direction speed ability) test [49]; (3) successfully complete a static proprioception and balance test consisting of standing on one leg with eyes closed for more than 30 s; and (4) followed by dynamic single-leg standing balance whilst flexing and extending the knee repeatedly for 15 s.

The primary outcome measure was the time needed for the athletes to return to their full pre-injury training level together with the duration of residual pain. The dynamic stability of the joint and AITFL scarring was also assessed as a secondary outcome measure using ultrasound, at 6 weeks post-injury.

Prior to enrolment, the study protocol was reviewed and received Institutional Review Board approval (IRB number: 0091-07-MMC, Meir Medical Center, Kfar-Saba, Israel).

Statistical analysis

Tegner activity level and RTP time were compared between groups using nonparametric analysis (Wilcoxon's nonparametric test). Clinical assessments of the lower extremity with the injured AITFL values were compared to healthy side and between intervention groups, in static (neutral [N]) and dynamic (IR and ER) positions, where appropriate. The results were compared using a *t* test and Pearson correlation. All statistical tests used two-sided *p* values, and the selected level of significance for all variables was $\alpha = 0.01$. SPSS statistical software (version 15.0, SPSS Inc, Chicago, Illinois) was used to analyse the data (Table 1).

Results

Median pre-injury Tegner activity level was 9 (range 7–10) for the PRP group and 9 (range 7–10) for the control group, (n.s.). At initial presentation, all patients had dynamic syndesmosis instability in the dorsiflexion—external rotation position (ER), and a significantly larger neutral (N) tibia–fibula distance compared to the contralateral uninjured ankle for all ankle positions. No difference was observed between groups with regard to injury severity before treatment, as observed dynamically on ultrasound examination or other imaging modalities (Table 2).

Mean RTP time was 40.8 ± 8.9 days for the PRP treatment group and 59.6 ± 12.0 days for the control group ($p = 0.006$) (Table 1). Six of the eight patients in the PRP treatment group were cleared to return to full unrestricted activity before the 6-week sonographic evaluation point; two PRP patients (of the three with the longest RTP time) had long delays between injury and presentation from injury to injection (10 and 11 days post-injury) and notably had long RTP times; Fig. 3). In the treatment group, only 12.5 % (1) of patients returned to play with pain compared to 62.5 % (5) of the control group. One patient in the control group complained of persistent pain, persistent subjective instability and disability and subsequently underwent a syndesmosis reconstruction procedure.

Median time from injury to PRP injection in the treatment group was 7.5 days (range 1–11). One patient in each group had also been diagnosed with a concomitant ATFL injury, and 2 patients in the control group presented with an

Table 2 Pre-treatment sonographic measurements of the injured and uninjured ankle in the treatment and control groups for all positions

	PRP group		Control group	
	Uninjured ankle	Injured ankle	Uninjured ankle	Injured ankle
Internal rotation	40.6 (5.8)[a]	48.0 (8.3)[a]	43.5 (5.7)[c]	53.4 (8.1)[c]
Neutral	41.3 (5.6)[b]	56.5 (15.1)[b]	43.4 (5.7)[d]	59.0 (6.0)[d]
External rotation	43.4 (5.6)[b]	67.1 (12.1)[b]	44.1 (5.6)[d]	72.9 (13.5)[d]

SS difference was seen, for each side and position, between non-injured and injured side, at base line [2-way ANOVA]

There was no difference between control and PRP groups

[a] For the PRP group, there was a significant difference ($p < 0.05$) between the uninjured ankle and treatment ankle at preliminary visit

[b] For the PRP group, there was a significant difference ($p < 0.001$) between the uninjured ankle and treatment ankle at preliminary visit

[c] For the standard treatment group, there was a significant difference ($p < 0.05$) between the uninjured ankle and treatment ankle at preliminary visit

[d] For the standard treatment group, there was a significant difference ($p < 0.001$) between the uninjured ankle and treatment ankle at preliminary visit

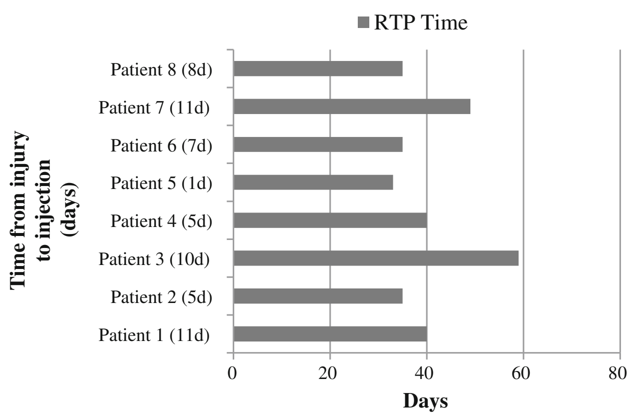


Fig. 3 RTP time according to time from injection in the PRP group

Table 3 Syndesmotic opening (standard deviation) for neutral, internal rotation, and external rotation by group and ankle at 6 weeks following treatment

	PRP		Standard treatment	
	Uninjured (SD)	Injured (SD)	Uninjured (SD)	Injured (SD)
Internal rotation	39.9 (7.0)	43.0 (6.9)	47.3 (3.5)	54.0 (5.2)
Neutral	40.4 (6.7)	45.4 (5.6)	47.0 (4.0)	57.7 (7.2)
External rotation	42.6 (6.7)[a]	48.6 (8.1)[a]	48.3 (3.1)[a]	63.7 (6.8)[a]

PRP to STD are not significant ($p > 0.05$)

[a] Uninjured to injured are significantly different for each position ($p < 0.001$)

additional grade 1 deltoid sprain. In this study, all patients but one in the control group returned to their previous performance level; however, the patients in the PRP treatment group did so in a significantly shorter period of time.

Sonographic evaluations showed differences ($p < 0.001$) in both the PRP treatment and the control groups (within the group), when comparing the injured and uninjured ankles in either position (IR, N, and ER) between base line and 6 weeks post-injury, as shown in Table 3. There was also a significant reduction of the tibio-fibular space in injured ankles at 6 weeks when compared to the initial presentation ($p = 0.025$), as shown in Table 4.

Discussion

The main findings of this study are that athletes receiving PRP injections for AITFL injury returned to play significantly sooner and also had significantly less pain than controls. Sonographic findings suggested that injured AITFL demonstrated improved healing compared to control injured athletes. This confirms that treatment with PRP can expedite the RTP of athletes with complete AITFL injuries.

Whilst soft tissue injuries represent the majority of injuries in sport, ligamentous injuries lead to long periods of absence from activity and there has been increased interest in new therapeutic modalities to facilitate faster and better healing. In the last decade, PRP therapies have emerged as novel treatment for the management of soft tissue injuries [32]. Basic science research and preliminary clinical data support the use of PRP-derived growth factors to improve cartilage healing [32] and in the management of soft tissue injuries [18, 22, 44, 59]. Platelets within the zone of injury are responsible for the release of biologically active factors, and PRP therapies are designed to enhance this process by delivering supra-physiologic concentrations of growth factors to the injured tissue in order to promote healing and speed recovery and function [3]. The use of PRP to promote healing has been reported for several soft tissue injuries [32, 36]. Mei-Dan et al. demonstrated the therapeutic value of PRP in the treatment of an acute grade 3 injury to the MCL of the elbow in an elite judoka, promoting a faster and complete healing response, as demonstrated by US, MRI, and an early return to competition [29]. Wetzel et al. have demonstrated significant reduction in pain and disability with PRP injections as treatment for proximal hamstrings injuries in athletes with complete return to sport [55]. Bubnov et al. showed PRP ultrasound-guided injections had a significantly higher level of pain relief, physical recovery, and faster regeneration compared with conventional conservative treatment in acute muscle trauma in professional athletes [9].

The kinematic biomechanical characteristics of the distal tibio-fibular syndesmosis are subtle and are coupled with the ankle joint [10, 48]. The syndesmosis widens between 1–2 mm when the foot is moved from plantar to dorsiflexion [40] . These subtle biomechanical changes of the intact syndesmosis make the clinical detection of syndesmotic instability difficult. Different clinical tests, such as the calf compression test (squeeze test) [24], the ER test [8], and the direct eversion manoeuvre, have been described to detect syndesmotic instability, with sensitivity ranging from 33 %-92 % [56]. Imaging, therefore, plays a key role in the detection of syndesmotic injury.

Weight bearing and stress radiographs of the tibio-fibular joint may appear normal in many injured ankles, but have low sensitivity and accuracy [50]. Spiral CT scans are sensitive for bony alignment and can identify up to 1 mm diastasis; however, they are not always readily available and are limited by cost together with concerns with radiation exposure [14, 51]. MRI is presently considered to be the standard imaging modality for syndesmotic disruption, but costs and availability do not warrant its routine use to evaluate every suspected syndesmotic injury [35, 37, 53].Ultrasound has been shown to be an excellent, consistent, reproducible, and accessible evaluation tool [31] . It provides a dynamic method to examine the AITFL, which is the hallmark of the sonographic assessment of the syndesmosis (Fig. 2).

In a recent study by Mei-Dan et al., normal sonographic values for the syndesmosis clear space were standardized and established as 3.8 mm $\pm$ 0.6 in neutral, 3.6 mm $\pm$ 0.6 in IR, and 4.1 mm $\pm$ 0.6 in ER [30]. The mean widening of the healthy tibio-fibular clear space was found to be 0.3 mm for ER–N and 0.4 mm for ER–IR. In neutral position, a measurement of 5.1 mm $\pm$ 0.6 signified 2 standard deviations above the mean, suggesting a measurement greater than this should be suspected as abnormal. Previous reports of syndesmosis injury outcomes and RTP guidelines relied solely on functional and clinical evaluations [16, 28, 52]. In the current study, repeated dynamic US evaluations were used in conjunction with physical examination and functional testing to assess the patients' clinical progression and provided an accessible, objective, and accurate tool for decision-making and enabling safe early RTP.

Numerous PRP preparation systems exist. The various systems differ in platelet collection efficiency and repeatability, final leucocyte count, platelet activation, and ease of use. PRP preparation systems are categorized into 3 methods: 1) double-spinning methods (producing 5–8 fold baseline levels platelet concentrations), 2) single-spinning methods (producing 1–3 fold baseline levels concentrations), and 3) selective blood filtration using commercial available technology. Platelet concentrates have also been categorized into pure platelet-rich plasma (P-PRP), in which leucocytes are purposely eliminated from the PRP, and leucocyte and platelet-rich plasma (L-PRP), containing high concentration of leucocytes [13]. The 'therapeutic dose' of PRP is considered at a range of 2–6 times above the normal baseline platelet count [1, 17, 20] to provide sufficient growth factors concentrations, but also in order to avoid an excessive fibrotic healing response which can be caused with elevated TGF levels [43]. The effect of leucocytes in the PRP preparation is controversial; however, basic science suggests that high leucocyte concentrations have a deleterious effect on acute soft tissue injuries. Pro-inflammatory proteases and acid hydrolases released from leucocytes may act as cytotoxic agents, causing secondary damage to the muscle tissue; the release of reactive oxygen species by neutrophils may act as an aggravating contributing factor [22].

A number of studies have focused on examining the effects of the local administration of single growth factors, such as platelet-derived growth factor BB (PDGF-BB) [54, 59], transforming growth factor β1 [38, 57, 59], or vascular endothelial growth factor (VEGF), [58] all of which may stimulate ligamentization. HGF activates both endothelial cell proliferation and migration and is a potent anti-fibrotic agent that could reduce scar formation [4]. PRGF is a single-spin, leucocyte-free preparation method which provides an effective endogenous method to transfer multiple cytokines and growth factors, including platelet-derived growth factor, transforming growth factor β1, and VEGF simultaneously to the injured ligament [3, 5, 6]. Previous basic research has indicated that autogenous tendon cells treated with PRGF have the potential for proliferation, collagen preservation, and remodeling [2, 6, 46]. Moreover, PRGF injections within the Achilles fascicles in a sheep model induced angiogenesis along with high cell density in one study [2] and has been shown to induce a more mature organization of collagen bundles, lower vascular densities, and decreased fibroblast densities in another study [Z-18], changes consistent with an accelerated healing process. Increased availability of VEGF and HGF at the site of injury can potentially promote the rapid formation of blood supply to the injured ligament and enhance cell migration, thus contributing to rapid remodeling. It has also been suggested that locally injected platelet-rich plasma serves as an activator of circulation-derived stem cells [26]. Another potential benefit of PRP use in this site of injury is the articular characteristics of the distal tibio-fibular joint [7, 15].

An important outcome measure when looking at high ankle sprain studies is time lost from sport. Significant variability exists between reports. Jones et al's analysis reported that time lost from sport due to syndesmotic sprains ranged from 0 to 137 days, with averages ranging from 10 to 14 days up to 52 days [25]. These ranges illustrate the variability in syndesmotic injury degree and severity, and the way these injuries are sometimes clustered in the literature in the same category, despite their significant differences. Hunt et al. reported a shorter RTP of a mean of 31.3 days away from intercollegiate American football for complete AITFL injuries [24]; however, no differentiation for syndesmotic instability or examination criteria were used. When dealing with high-level competitive athletes, RTP time plays an important role and, in the more severe syndesmosis injuries, surgical treatment is occasionally necessary. Taylor et al. have shown that in selective cases, athletes can return to full activity as early as 6 weeks after internal fixation of grade III syndesmosis sprains [52]. Recognition of the injury type and grade is, therefore, imperative and assists in the optimal treatment and prediction of time lost from sport. In this study, patients sustained a complete AITFL disruption (grade 3 AITFL injury). One patient in each group had also been diagnosed with a concomitant ATFL injury, which had healed by the 6 week follow-up and did not prolong the time lost from sports. Two patients in the control group presented with an additional deltoid sprain, one of which had the shortest RTP time yielding the only RTP time that actually equaled the PRP group. The other subject needed a syndesmosis reconstructive surgery, but follow-up US at 6 weeks showed a completely healed deltoid. Partial ATFL or deltoid strains did not influence either the dynamic US examination or RTP time in these cases. Our research has demonstrated an average return to sport time of 41 days for the treatment group versus 60 days for the control group, an improvement of 19 days. This PRP treatment allowed athletes to return to training and competition faster without the need to undergo surgery and with less pain than in the control group. Although no further formal follow-up was performed for the study participants, their regular sports medical staff was contacted, and no re-injuries were registered for a minimum of 2 years after the conclusion of the study. A treatment allowing a significant decrease in return to pain-free activity after a ligament injury is applicable to elite athletes, recreational athletes, or non-athletes, for example, labourers injured on the job. Further research into PRP treatment and the effect on return to activity may allow expansion of indications for ligament injuries to other areas of the body.

There are several limitations to this study, the most significant being the small number of patients in each group. This is attributed to the uncommon occurrence of high ankle sprains and the elite sports activity of the cohort. Despite the small numbers studied, RTP time was significantly shorter in those athletes treated with PRP injections and a functional rehabilitation protocol. The sonographic tibio-fibular space widening at 6 weeks was significantly reduced compared to widening following injury for the injured ankles in the PRP group, compared to the controls. The small sample size was, however, not sufficient to show statistical significance in sonographic dynamic opening in ER of the healed injured ankles between groups. A post hoc power calculation showed that 15 patients would be needed in each group to predict a 30 % statistically significant change (difference between groups) with alpha set at 0.05 and beta of 0.80. There was, however, still a significant difference in sonography at 6 weeks, between the injured and the uninjured ankle in both treatment groups (Table 3). This is reasonable as this period of time may still be considered within the remodeling phase of the healing process. It is important to remember that substantial soft tissue injuries are likely to result in scar tissue, which could alter the anatomical appearance, orientation, and biomechanical properties of the healing ligament. One of the potential goals of PRP in these types of injuries is to minimize the extent of scar tissue formation and promote a healing response, which would restore as normal tissue properties as possible. As the most important outcome in this type of population of elite level athletes is their ability to return to pre-injury level of activity, these sonographic differences did not seem to be clinically significant. Another limitation is the lack of blinding of the athletes to treatment, which could potentially bias the recovery and return to sport.

There was variability in the time of initial PRP administration from injury in the treatment group. Reasons included delayed recognition by primary team physicians, tertiary referral, and injuries sustained overseas by local athletes. However, beneficial results were observed with administration up to 11 days post-injury. The biological explanation lies in the chronology of ligament healing, which has been separated into 3 distinct phases (based on a completely ruptured ligament): inflammatory, reparative, and remodeling. The initial response to injury would be the

Table 4 Comparison of injured ankle at baseline vs. injured ankle at 6w

	PRP group		Control group	
	Injured side T0	Injured side 6W	Injured side T0	Injured side 6W
Internal rotation	48.1 (2.5)	43.0 (6.9)	50.7 (7.2)	54.0 (5.2)
Neutral	53.9 (6.9)	45.4 (5.6)	58.0 (9.8)	57.7 (7.2)
External rotation	65.9 (3.6)[a]	48.6 (8.1)[a]	74.0 (16.7)[a]	63.7 (6.8)[a]

Although a trend is seen (ER0-ER6: PRP = 17.3, SD = 10.3), with these numbers no significant interaction between time and treatment are present between groups

[a] There was a significant difference ($p < 0.05$) between preliminary visit and 6-week follow-up

acute inflammatory phase, lasting 24–72 h. The reparative phase of healing begins 3–5 days post-injury, and the remodeling phase of healing begins 15–28 days post-injury. PRP provides a better environment and promotes more tissue organization and prevents of excessive scar tissue formation. The time frame to locally influence the healing environment may be for as long as 10–12 days from the time of injury, before the remodeling process is fully committed although treatment may be optimally initiated 2–5 days post-injury [36]. It is, therefore, reasonable to expect a faster healing response and RTP if all subjects in the PRP group had been injected within a week from injury. In this study, patients who were diagnosed and treated earlier presented tended to have shorter RTP times (Fig. 3). This observation suggests that PRP may have an optimal effect during the early stages of the reparative phase.

The method of PRP preparation should be considered, when applying these findings. Plasma rich in growth factors is a relatively inexpensive concentrate, prepared manually resulting in pure PRP, with 2 to 3 times the blood platelet count and no white blood cells, in contrast to PRP produced by many commercially available preparation systems. The frequency of injections, volumes, and activation methods also needs to be appreciated and; therefore, the findings of this study cannot be extended to patients treated with other PRP-applied techniques or protocols.

Conclusions

Athletes suffering from high ankle sprain benefit from PRP ultrasound-guided injections and should expect a shorter RTP time/time lost from sport and a rapid stabilization of the syndesmosis joint, with diminished long-term residual pain.

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