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TITLE

Clinical effects of image-guided hyaluronate injections for the osteochondral lesions of ankle in sport active population

AUTHORS

Marco Di Gesù,[1] Augusto Fusco,[2] Angelo Vetro,[1] Marco Iosa,[2] Fabrizio Mantia,[1] Angelo Iovane[3], Roberto Mantia[1]

[1] Centro Medico Mantia, Palermo, Italy

[2] Clinical Laboratory of Experimental Neurorehabilitation, IRCCS Fondazione Santa Lucia, Rome, Italy

[3] Policlinico Universitario "P. Giaccone", Palermo, Italy

Corresponding author

Augusto Fusco, Ph.D.

Clinical Laboratory of Experimental Neurorehabilitation

IRCCS Fondazione Santa Lucia

Via Ardeatina 306

00179 Rome, Italy

Ph: +39-06-51501077

Fax: +39-06-51501004

Email: a.fusco@hsantalucia.it

ABSTRACT

BACKGROUND: Hyaluronic acid injections are effective as intra-articular treatment, but their use in the ankle has been hindered for the difficulty of execution in this area. Use of a guidance of musculo-skeleletal ultrasound could improve the success rate and the subsequent clinical outcome, for the ameliorating placement of the needle tip. The aim of this pilot study was to assess the short-term efficacy in terms of functional outcomes and pain of a image-guided intra-articular hyaluronic acid injections of post-traumatic osteochondral lesions (OLs) of the ankle.

METHODS: Thirty sport active patients (21 males; mean age 27.6±7.46) with a clinical and radiological diagnosis of post-traumatic ankle OLs at initial stage, received a course of three injections within a month. Patients were evaluated for pain (with Numerical Rating Scale, NRS) e function (Ankle-Hindfoot Scale, AHS, and range of motion, ROM) before every injection and ninety days after the last injection (T0-T3).

RESULTS: Pain showed a significant and clinically relevant improvement during the period of treatment ($p<0.001$), even if pain was still presented at last follow-up assessment. Also for AHS e ROM, it was recorded a similar positive trend during time ($p<0.001$ for both measurements). Before intervention, pain and function resulted correlated ($p<0.001$), while at follow-up assessment these correlations were reduced, remaining only between pain at rest and plantar-flexion range.

CONCLUSION: These results showed positive effects of the intra-articular hyaluronic acid for the osteochondral lesions, with a full recovery of the functional activity and a significant reduction of pain.

KEY WORDS: Rehabilitation; Sport; Conservative Treatments; Musculo-Skeletal Ultrasound; Hyaluronic Acid.

INTRODUCTION

Ankle is commonly affected by inflammatory processes, involving cartilage and the subchondral bone with a subsequent degeneration of the articular surface. This leads to a long-term chondropathy with the onset of chronic pain and functional impairments, that restricts particularly the sport activity in active population [1]. Several terms have been used to describe these pathological conditions, but "osteochondral lesions" (OLs) seem remain the most inclusive to describe all these features [2]. Etiology is still unclear but most of OLs may be addressed to a repetitive trauma, even if it has been described also in absence of any traumatic condition [2]. The OLs have been described in 6.5% of ankle sprains, but this incidence is considered underrated due to the subclinical characteristic or missing diagnosis, especially in the initial phases of the disease [3]. Conservative treatments should be fully exploited before surgery. Rehabilitation usually starts after an initial period of rest and/or restriction from sport activity, in association with pharmacological medication and/or intra-articular injections [4].

In the last decade, strong evidences have proved as hyaluronic acid (HA) injections are valid treatments for all joints [5,6]. HA is formed by a high molecular weight polysaccharide, present in the human cartilage as a component of synovial fluid and extracellular matrix. It contributes to the elasticity and viscosity of synovial fluid, acts as a fluid shock absorber, helping to maintain the structural and functional features of the cartilage matrix [5]. Furthermore, it may play a role in the inhibition of the production and releasing of prostaglandins, inducing proteoglycan aggregation and synthesis, and modulating the inflammatory response [5]. It has been also demonstrated to increase significantly total cartilage volume [7].

Notwithstanding the large use of intra-articular injections with HA, there are few studies for the ankle compartment, especially if compared with the great amount of research trials for hip and knee. One of the possible reasons could be related to the anatomical landmarks, that are less reliable in the ankle. It has been noted as the success rate of the intra-articular injections and the clinical improvement may depend by the accurate placement of the needle tip into the joint, in addition to the type of administered medication and type of performed rehabilitation [8]. For the improvement of targeting, in recent years it is growing the use of musculo-skeleletal ultrasound (MSUS) as guidance to execute intra-articular injections. Its application is quick, easy to use, repeatable, well accepted by patients and without side effects [9]. It is not well known as the guidance of MSUS in the HA injections could affect in performing this treatment in the ankle. At the best of our knowledge, no analogues studies have been performed for the OLs.

The purpose of this study was to assess the functional outcomes of a course of image-guided hyaluronic acid intra-articular injections for the treatment of post-traumatic osteochondral lesion of the ankle at initial phase. To achieve this aim, we have evaluated the pain relief and the motor and functional recovery of the ankle in sport-active population. We have also investigated the factors influencing the potential efficacy of this treatment and the correlations among the recorded measures.

MATERIAL & METHODS

Participants

Patients were admitted to an outpatient ambulatory due to pain and limitation of movement to the ankle. We included patients with the following characteristics: eighteen years of age or older; diagnosis of post-traumatic ankle OLs with chronic pain longer than one month; a definition of stage 1 of OLs at Magnetic Resonance Imaging (MRI) scan; performed sport activity three times a week at least, before the beginning of the symptoms; mild to moderate discomfort in the physical activity; no evidence of underlying fracture or bone oedema. Exclusion criteria were: treatment with HA preparations within six months previous to study enrollment; significant effusions of the ankle; previous intra-articular injections of the ankle; rheumatic inflammatory joint diseases; joint infections or poor skin condition which may have caused following infections; hypersensitivity to HA preparations, avian proteins, feather and egg products or a general contraindication to local HA injection; previous surgery of the foot and pregnant or lactating women. All patients gave informed consent prior to the treatment.

Imaging Assessment

Before the intra-articular injection, a MRI scan was performed to establish the diagnosis and the radiological features. The MRI assessment (GE Signa Excite HD®, Milwaukee, WI, USA) was performed at 1,5 Tesla through cartilage-sensitive sequences such as fat suppressed, T1-weighted gradient echo (GE), T2-weighted and STIR sequences. GE sequences improves signal sensitivity when small structures are imaged. Fast Spin GE sequences provide T1-weighted images where the intra-articular fluid is less intense than the cartilage and fat is suppressed therefore maximizing the contrast between cartilage, fluid and marrow, with cartilage showing a bright signal.

The MRI scan has shown a high specific and positive predictive value in diagnosing OLs, improving the accuracy of the diagnosis [10]. Hepple, Winson and Glew have conceived a staging system for OLs based on the MRI, indicating the initial phase (stage 1) the articular cartilage damage only [11]. In our study, a preliminary MRI scan permitted the exact definition of the clinical diagnosis.

Treatment

Patients were undergone to a course of ultrasound image-guided three injections of sodium hyaluronate (Artz®, concentration 25 mg/ml, WM 800-1170 kDa), after betadine preparation using an anterior approach with a 20-Gauge spinal needle (Figure 1). The ultrasound examination (Technos MPX, Esaote Spa, Genoa, Italy) was performed by the same radiologist, using a linear transducer (13 MHz). The capsule was assessed by color power Doppler for blood flow (recorded as absent or present). Injections were always administered by the same experienced physician. Patients were positioned supine, with the knee flexed and the foot flat on the plinth. Ankle was placed in plantar flexion, opening the anterior side of the joint. If present, mild joint effusion were aspirated before injection to prevent dilution of the HA. Excessive weight bearing and strenuous physical activities were discouraged for 48 h after each injection.

Evaluation and Outcome Measures

A detailed history and physical examination were gathered at the initial visit for the assessment of post-traumatic ankle OL. Age, gender, and side effects were recorded.

Clinical assessments were carried out at baseline (T0 – before the first injection), after seven days (T1 – before second injection), thirty days (T2 – before third injection) and ninety days (T3 – follow up period). At all evaluations, the following instruments of assessment were applied: the

Ankle-Hindfoot Scale, range of motion of the ankle, 11-point Verbal Numerical Rating Scale (VNRS) for pain at rest ($VNRS_r$) and after twenty meters of natural walking ($VNRS_w$).

The VNRS is an 11-point scale that measures pain severity. Patients were instructed to express their pain in terms of 0-10 values, where a score of 0 represents no pain at all and a score of 10 represents the worst pain imaginable. This scale has been shown to have acceptable measurement properties (reliable, generalizable and internally consistent) for pain intensity in both clinical and experimental settings [12].

The Ankle-Hindfoot Scale (AHS), developed by the American Orthopaedic Foot and Ankle Society, was used to assess pain, function and alignment. This scale has a 100-point clinical rating score, with the maximum indicating the patient's pain-free, full range of motion, good stability and alignment and full capacity of walking without any aids or activity limitations [13].

Dorsi–flexion and plantar–flexion were measured and described as sagittal range of motion (ROM). The measurements were obtained using a universal goniometer, which has been demonstrated to be a reliable tool for measuring ROM. The two axis of goniometer were placed parallel to the main axis of tibia and foot in sagittal plane and this measure was performed by the same expert physician.

Statistical Analysis

We calculated the medians, quartiles and ranges for the used scales (VNRS e AHS), and their means and standard deviations. We compared the results using non-parametric tests (Friedman's test). An analysis of variance (ANOVA) was performed on the ankle range of motion using gender (male vs female) and age (<30 vs ≥ 30years old) as between subject factors and the 4 assessments as the within subject factor. For VNRS and AHS the effectiveness of the intervention was also measured, as previously performed in other analogues studies [14,15]. It reflects the proportion of potential improvement that was achieved between T0 and T3, calculated as [(T3 score − T0 score)/(maximum score − T0 score)] × 100. Thus, if a patient achieved the highest possible score after intervention, the effectiveness was 100%.

Spearman coefficient (ρ) was used to evaluate the correlation between AHS and the other assessments. A probability value of 0.05 was set as the level of statistical significance. Data analysis was performed using the SPSS 17.0.

RESULTS

Thirty patients (21 Male; 9 female) matched the inclusion criteria and they were selected for this study. Mean age was 27.6 (±7.46 SD). All of them were referred to a clinical and radiological diagnosis of post-traumatic ankle OLs, with symptoms from 1 month to 18 months before. Pain showed a significant reduction during the period of treatment (χ^2=79,97, p<0.001). All patients complained the presence of pain at the end of treatment and at last follow-up, both at rest and after walking, even if significantly reduced. Median of $VNRS_r$ score was 8 (1st and 3rd quartiles: 7-9) at T0, 5 at T1 (3-5), 3 at T2 (3-5) and, finally, 2 at T3 (1-2). Analogously, $VNRS_w$ score performed after walk demonstrated a significant amelioration (χ^2=82,94, p<0.001). Median of $VNRS_w$ was 8,5 (1st and 3rd quartiles: 7-9) at T0, 5 at T1 (4-7), 4 at T2 (4-5) and, finally, 2 at T3 (2-2), as shown in Figure 2. These improvements were higher than that of two-points or 30% considered to be clinically important.

Similarly, also the AHS presented a similar trend during time (χ^2=87,19, p<0.001). Recorded medians were 52 (1st and 3rd quartiles: 30-52) at T0, 74 at T1 (25-75), 88 at T2 (87-88) and 98 at T3 (98-98). Also the ankle ROM showed a significant improvement both for dorsi-flexion (χ^2=59,19, p<0.001) and for plantar flexion (χ^2=49,1, p<0.001), with the recovery of full ROM at the last evaluation. Repeated measure analysis of variance showed a significant improvement of ankle

ROM in terms of dorsi-flexion along time (+7°, F=27.17, p<0.001), without any significant main effects of gender (F=0.05, p=0.821) or age (F=0.74, p=0.396), nor of their interactions (p>0.3 for all of them). On the other hand, the improvement in terms of plantar-flexion along time (+7°, F=29.30, p<0.001) was found quite different between males (+5°) and females (+12°, interaction gender per time F=4.43, p=0.006). A main effect of age was also found significant (F=4.93, p=0.035), with wider plantar-flexion for subjects under 30 years old (8° vs 6°).

The effectiveness was of 78.6±7.6% for the $VNRS_r$ and quite, but significantly slower (p=0.018, paired t-test) for the $VNRS_w$: 75.7±7.9%. The effectiveness recorded in terms of AHS was very high (96.5±2.9%). None of these parameters resulted affected by age or gender.

Before intervention, the AHS were significantly correlated with the $VNRS_r$ (ρ=-0.893, p<0.001); $VNRS_w$ (ρ=-0.751, p<0.001), range of dorsi-flexion (ρ=0.458, p=0.011), range of plantar-flexion (ρ=0.731, p<0.001). After the first injection (T1), this correlation was found quite lower than before it (with $VNRS_r$ ρ=-0.593, with $VNRS_w$ ρ=-0.490) and not significant neither for dorsi-flexion range (p=0.420) nor for plantar-flexion range (p=0.052). At follow-up, it was more reduced, remaining only those with $VNRS_r$ (ρ=-0.370, p=0.044) and plantar-flexion range (ρ=0.381, p=0.038) still significant, but not those with $VNRS_w$ (ρ=-0.283, p=0.129) and dorsi-flexion range (ρ=0.318, p=0.087).

DISCUSSION

The present study was conducted to establish the outcomes after a course of ultrasound-guided intra-articular injections with Hyaluronic Acid in post-traumatic osteochondral lesion of the ankle. To the best of our knowledge, this is the first case of HA intra-articular injections with MSUS guidance for the treatment osteochondral lesions at initial phase. Our results suggest that this treatment is useful in the relief of pain and for the full recovery of the ankle.

In our study, pain was of relevant intensity at the first evaluation and highly correlated with the functional impairment (as assessed by means of the AHS and range of motion). At the last follow-up, mild pain was still present even if greatly reduced, but it did not result correlated with the ankle disability. The function of the ankle was nearly full, both in terms of activity and range of motion, even if it was not fully recovered in some patients. A slight effect of gender was observed for the recovery of dorsi-flexion range of motion, with women more responsive to the treatment. It could be due to their reduced anthropometric measures. The effect of age was noted as a main effect affecting the range of motion, but the absence of significant interactions with treatment showed that the intervention was effective in similar manner for all the subjects.

These results confirmed a previous study, that assessed a short term efficacy in reducing pain and disability of Platelets Rich Plasma (PRP) injections in comparison with HA injections without any image guidance [16]. This study reported a significant improvement of functional outcomes and pain for both treatments (a course of three injections with HA or PRP). Even if the OLs were worse (until grade 3 according to Ferkel classification) [17], the total scores for pain, assessed with VAS, and functional disability, evaluated by means of AHS, were similar during the different assessments (4 weeks, corresponding about our T2, and 12 weeks, corresponding about our T3). Respect to our study, Mei-Dan and colleagues performed another follow-up assessment at 28 weeks after the first injection, maintaining the achieved results both in terms of pain and functional outcomes.

Our study strengthens the assumption of using HA injections as a valuable treatment to approach to chondropathies at all [5]. At the light of our findings, also patients with OLs at initial phase were benefited by this type of treatment. Repetitive injections were needed to maintain a significant reduction of pain and the functional improvement on the ankle. In an early phase of OLs, with the presence of the only cartilage damage, intra-articular viscosupplementation may provide to supply exogenous hyaluronate into the synovial joints to restore the normal rheological environment in joints [2,5]. The rationale for the use of HA is based not only on the concept of "fluid replacement" but also on the biological activation [18]. These effects are effective in decreasing the disease progression. Other accepted products for intra-articular injection, as corticosteroid, are limited in widespread use for the controversial short-term outcomes and adverse effects [19].

Another possible reason of the efficacy of this treatment could be related to the young age of our sample. Most of the OLs at initial stage are diagnosed between 20 and 30 years of age [2,3], probably due to the post-traumatic origin [20]. Targeting the treatment towards a sport-active population, it could have made the HA valid in OLs in this study. At the same time, the presence of a minimal clinical important difference in our results strengthens the obtained outcomes also in terms of functional recovery. The treatment achieves the threshold a minimal clinical important difference in the outcomes already before the second injection (at T1), even if we noted a cumulative effect of the 3 injections. The lack of important systemic adverse or side effects of HA allows a sustainable use of this treatment, also in the OLs [21]. It is important to note that pain was not totally disappeared in our study, with a minimal discomfort still present after the HA course of injections (but reduced for about 75%). So, a period of rehabilitation may be necessary to complete the full recovery from impairments and pain.

Finally, it is conceivable that the use of MSUS to guide the intra-articular injections has had a helpful role in the accuracy of the treatment and in the achievement of the obtained outcomes. Recent studies are suggested as the ultrasound guidance leads to a more effective treatment with respect to blind injections [22,23], especially for the intra-articular treatment in sport [24].

Our results have to read at the light of their limitations. The most important limit was related to the lack of placebo group or control group underwent to an analogous treatment. In this pilot study, we have tested only the efficacy of a course of image-guided HA injections. To verify this aim, we have included a quite large sample size. As well, double-blind, controlled studies should be performed with longer follow-up assessments to assess the maintenance of the outcomes during time. Use of methodological studies could clarify the correct medical behavior in the early phases of OL. Then, prospective studies should point out the possible influences and relations with other musculoskeletal conditions, incorporating the functional impact of treatment by means of well-validated outcome's measures [14,25]. This could be useful also to verify the short and long term benefit and cost-effectiveness of image-guided injections (alone or in comparison with pharmacological or rehabilitative treatments).

Despite these limitations, this study clearly shows the short-term benefit achieved by means of a course of three Hyaluronic Acid injections, guided by the guidance of musculo-skeletal ultrasounds, in the treatment of ankle osteochondral lesions at initial stage, with reduction of pain and recovery of functional activity.

REFERENCES

1. Amor B, Dougados M, Kahn MA. Management of refractory ankylosing spondylitis and related spondyloarthropathies. Rheum Dis Clin North Am 1995; 21:117–28.
2. Chew KT, Tay E, Wong YS. Osteochondral lesions of the talus. Ann Acad Med Singapore 2008; 37:63-8.
3. Verhagen RA, Maas M, Dijkgraaf MG, Tol JL, Krips R, van Dijk CN. Prospective study on diagnostic strategies in osteochondral lesions of the talus: Is MRI superior to helical CT? J Bone Joint Surg Br 2005; 87:41-6.
4. Shearer C, Loomer R, Clement D. Nonoperatively managed stage 5 osteochondral talar lesions. Foot Ankle Int 2002; 23:651-4.
5. Foti C, Cisari C, Carda S, Giordan N, Rocco A, Frizziero A, Della Bella G. A prospective observational study of the clinical efficacy and safety of intra-articular sodium hyaluronate in synovial joints with osteoarthritis. Eur J Phys Rehabil Med 2011; 47:407-415.
6. Guarda-Nardini L, Cadorin C, Frizziero A, Ferronato G, Manfredini D. Comparison of 2 hyaluronic acid drugs for the treatment of temporomandibular joint osteoarthritis. J Oral Maxillofac Surg 2012;70:2522-2530.
7. Chareancholvanich K, Pornrattanamaneewong C, Narkbunnam R. Increased cartilage volume after injection of hyaluronic acid in osteoarthritis knee patients who underwent high tibial osteotomy. Knee Surg Sports Traumatol Arthrosc 2014; 22:1415-23.
8. Hall S, Buchbinder R. Do imaging methods that guide needle placement improve outcome? Ann Rheum Dis 2004; 63:1007–8.
9. Naredo E, Cabero F, Beneyto P, et al. A randomized comparative study of short-term response to blind injection versus sonographic-guided injection of local corticosteroids in patients with painful shoulder. J Rheumatol 2004; 31:308–14.

10. Joshy S, Abdulkadir U, Chaganti S, Sullivan B, Hariharan K. Accuracy of MRI scan in the diagnosis of ligamentous and chondral pathology in the ankle. Foot Ankle Surg 2010; 16:78–80.
11. Hepple S, Winson IG, Glew D. Osteochondral lesions of the talus: a revised classification. Foot Ankle Int 1999; 20:789–793.
12. Breivik EK, Bjornsson GA, Skovlund E. A comparison of pain rating scales by sampling from clinical trial data. Clin J Pain 2000; 16:22–8.
13. Kitaoka HB, Alexander IJ, Adelaar RS, Nunley JA, Myerson MS, Sanders M. Clinical rating systems for the ankle-hindfoot, midfoot, hallux, and lesser toes. Foot Ankle Int 1994; 15:349–53.
14. Paolucci T, Fusco A, Iosa M, et al. The efficacy of a perceptive rehabilitation on postural control in patients with chronic nonspecific low back pain. Int J Rehabil Res 2012; 35:360-6.
15. Fusco A, Iosa M, Venturiero V, et al. After vs. priming effects of anodal transcranial direct current stimulation on upper extremity motor recovery in patients with subacute stroke. Restor Neurol Neurosci. 2014;32(2):301-12.
16. Mei-Dan O, Carmont MR, Laver L, Mann G, Maffulli N, Nyska M. Platelet-rich plasma or hyaluronate in the management of osteochondral lesions of the talus. Am J Sports Med 2012; 40:534-41.
17. Ferkel RD, Zanotti RM, Komenda GA, Sgaglione NA, Cheng MS, Applegate GR, Dopirak RM. Arthroscopic treatment of chronic osteochondral lesions of the talus: long-term results. Am J Sports Med 2008; 36:1750-62.
18. Sun SF, Chou YJ, Hsu CW, Chen WL. Hyaluronic acid as a treatment for ankle osteoarthritis. Curr Rev Musculoskelet Med 2009; 2:78–82.
19. Plant MJ, Borg AA, Dziedzic K, Saklatvala J, Dawes PT. Radiographic patterns and response to corticosteroid hip injection. Ann Rheum Dis 1997;56:476-480.

20. Valderrabano V, Horisberger M, Russell I, Dougall H, Hintermann B. Etiology of ankle osteoarthritis. Clin Orthop Relat Res 2009; 467:1800–6.

21. Page J, Henry D. Consumption of NSAIDs and development of congestive heart failure in elderly patients: an underrecognized public health problem. Arch Intern Med 2000; 160:777-84.

22. Bum Park Y, Ah Choi W, Kim YK, Chul Lee S, Hae Lee J. Accuracy of blind versus ultrasound-guided suprapatellar bursal injection. J Clin Ultrasound 2012; 40:20-5.

23. Van den Bekerom M, Lamme B, Sermon A, Mulier M. What is the evidence for viscosupplementation in the treatment of patients with hip osteoarthritis? Systemic review of the literature. Arch Orthop Trauma Surg 2008;128:815-823.

24. Hall MM. The accuracy and efficacy of palpation versus image-guided peripheral injections in sports medicine. Curr Sports Med Rep 2013; 12:296-303.

25. Morone G, Iosa M, Paolucci T, et al. Efficacy of perceptive rehabilitation in the treatment of chronic nonspecific low back pain through a new tool: a randomized clinical study. Clin Rehabil 2012; 26:339-50.

FIGURE LEGENDS

Figure 1

Transversal plane ultrasound-guided injection. The needle, positioned with the linear transducer, is inserted obliquetly into the anterior recess of the talo-tibial joint. The patient lied supine with the knee flexed and the foot flat on the plinth. Ankle was placed in plantar flexion, opening the anterior side of the joint. Mild joint effusion, if present, were aspirated before injection to prevent dilution.

Figure 2

Box and whisker plot for $VNRS_r$ *(above, left column) and* $VNRS_w$ *(below, left column), maximum ankle Dorsi-Flexion (above, middle column), maximum ankle Plantar-Flexion (below, middle column), AHS (above, right column) in the four evaluation-times. The lines of the box shows the lower quartile, median (bold line), and upper quartile values. Whiskers represents the most extreme values within 1.5 times the interquartile range from the ends of the box. Black circles represent the outliers (data with values beyond the ends of the whiskers).*

TABLE LEGENDS

Table 1

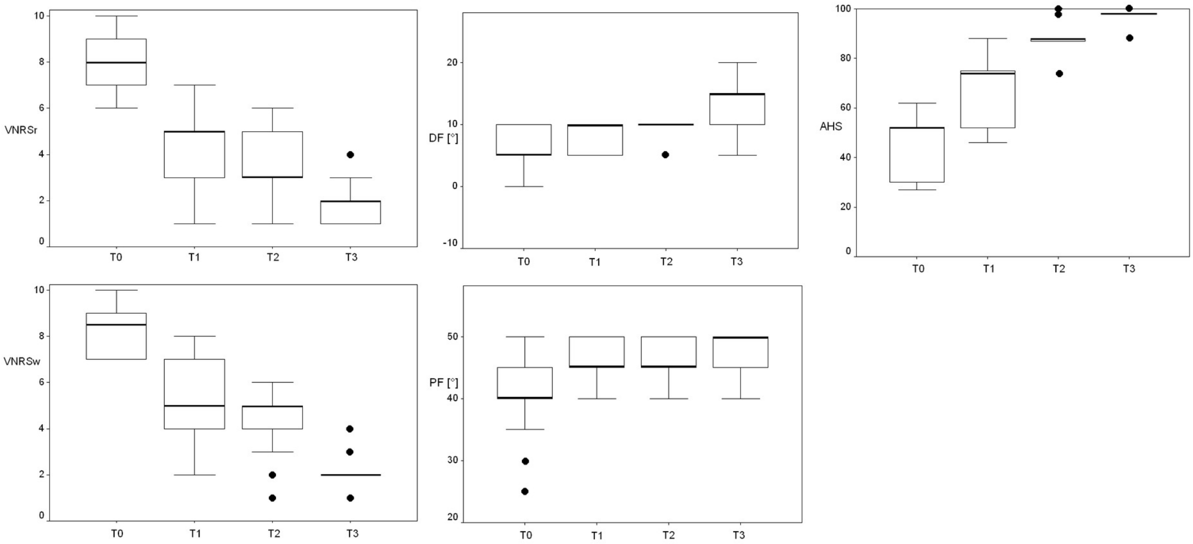
Spearman Correlation Coefficient (r) and relevant p-values between AHS and the other parameters recorded in the four evaluations.

Table 2

Results of Repeated Measure ANOVA on dorsi- (DF) and plantar-flexion (PF).

Correlation with AHS		$VNRS_r$	$VNRS_w$	DF	PF
Time	T0	ρ=-0.893, p<0.001	ρ=-0.751, p<0.001	ρ=0.458, p=0.011	ρ=0.731, p<0.001
	T1	ρ=-0.592, p=0.001	ρ=-0.490, p=0.006	ρ=-0.153, p=0.420	ρ=0.358, p=0.052
	T2	ρ=-0.444, p=0.014	ρ=-0.257, p=0.171	ρ=0.115, p=0.544	ρ=0.102, p=0.591
	T3	ρ=-0.370, p=0.044	ρ=-0.283, p=0.129	ρ=0.318, p=0.087	ρ=0.381, p=0.038

Parameter	Age	Gender	Time	Age*Gender	Age*Time	Gender*Time	Age*Gender*Time
DF	F=0.744 p=0.396	F=0.052 p=0.821	F=27.166 p<0.001	F=0.385 p=0.540	F=0.512 p=0.675	F=0.766 p=0.517	F=1.177 p=0.324
PF	F=4.934 p=0.035	F=0.036 p=0.380	F=29.303 p<0.001	F=0.380 p=0.543	F=0.451 p=0.717	F=4.437 p=0.006	F=0.473 p=0.702


VNRSr
10
8
6
4
2
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T0
T1
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DF [°]
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-10
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T2
T3
AHS
100
80
60
40
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0
T0
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T2
T3
VNRSw
10
8
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T0
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T3
PF [°]
50
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T0
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T3