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Efficacy of Shock Waves Combined with Adjuvant Therapy with Tendon Supplement in the Treatment of Plantar Fasciitis: A Prospective Randomized Study

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Abstract Physical treatment with focused shock waves is effective in the treatment of tendonitis in 60-90% of cases. Plantar fasciitis is attributable to the group of tendon pathologies for its degenerative-inflammatory anatomopathological characteristics. Food supplements could facilitate the healing of tendinopathies when combined with shock wave therapy. We designed a single-blind, randomized prospective study (level of evidence IB). Forty-four patients with plantar fasciitis were recruited and randomized to group A (18 patients) and group B (26 patients), where they were treated with focused shock waves alone and the combination of focused shock waves and tendon supplement, respectively. Statistically significant improvement in pain remission (primary endpoint) and functional recovery (secondary endpoint) occurred in both groups at three time points of the monitoring (Months 0, 3, and 6). The time-group interaction analysis confirmed the best efficacy of the combination treatment with shockwave and supplement (group B). The results of this study demonstrate a positive therapeutic effect of the combination of focused shock wave therapy and a complex tendon supplement in the treatment of plantar fasciitis.

Keywords: *focused shock waves, tendinitis, nutraceuticals, plantar fasciitis*

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1. Introduction

Plantar fasciitis is a common degenerative and inflammatory pathology affecting the plantar fascia and has several similarities with tendinopathy [1]. About 10% of the population had this disease, which is more common in women between the ages of 40 and 70 [2], and it progresses into chronic pain in 10-20% of cases [1]. This condition is often positively managed with conservative treatments, such as physical therapies, systemic non-steroidal anti-inflammatory drugs, local corticosteroid injections, unloading with shoe inserts. However, in non-responder cases, plantar fascia release surgery with the regeneration of the calcaneal bone-tendon junction can be recommended [3,4,5,6].

Structurally, tendons and musculotendinous fasciae are composed of a cellular part and a fibrillar part surrounded and located in an extracellular matrix [7]. The cells are mainly fibroblasts and produce the extracellular matrix components: collagen fibers, elastin fibers, and proteoglycans. When a patient presents with tendinopathy or fasciitis, the degenerative component tends to prevail or alternates with the inflammatory component. The most important biohistochemical changes of the microenvironment include hypoxia with cell necrosis, an increase of metalloproteinases that stimulate the degeneration of the matrix, over-production of inflammatory cytokines, the predominance of type III over type I collagen fibers resulting in more significant ultrastructural disorganization of the fibers, increased VEGF expression that promotes local neoangiogenesis and progressive calcific metaplasia which replaces the degenerated tissue [8].

Extracorporeal focused shock wave therapy (ESWT) has recently become very popular and is used to treat many soft tissue disorders [9]. The shock waves can be characterized by a rapid rise in pressure, followed by an equally rapid descent in a short period of time, which justifies its cavitation effect. One potential benefit is that the flow of energy is focused on a small area where the neoangiogenic, revascularizing, analgesic, inflammation

modulation, and proliferative therapeutic effects will be concentrated [10].

In recent years, the use of nutraceuticals has been suggested to support the physiological turnover of tendon to counteract and modulate inflammation and local degeneration [11] using numerous tendon-protective substances such as arginine, methylsulfonylmethane, collagen, vitamin C, vitamin D, amino acids, bromelain, glucosamine, and chondroitin sulfate [12,13,14]. Several studies suggest that oral supplements increase the precence of these compounds in the tendon context and may help preserve the damaged structures [15]. Their efficacy has been demonstrated by pre-clinical studies and randomized controlled trials (RCTs) [16], but few have verified the efficacy of focused shockwaves combined with food supplements.

This study aims to verify whether combination treatment with shock waves and tendon supplement is efficient on pain (primary endpoint) and can achieve a better functional recovery (secondary endpoint) in patients with plantar fasciitis.

2. Materials and Methods

2.1. Study Design and Population

We designed a prospective randomized, single-blind study with an evidence level of 1B, which was approved by the local Ethics Committee (number 5980 on 11.09.2019) and registered at ClinicaTrials.gov (NCT04664712). The subjects enrolled signed informed consent.

Forty-four patients were enrolled at the Osteoporosis-Densitometry-Shockwave Outpatient Clinic of the Orthopedics and Traumatology Unit of the "Policlinico" University Hospital of Bari. Of these patients, 18 and 26 patients were randomized in Groups A (shock wave therapy) and B (shock wave therapy and tendon supplement), respectively. In these two groups, the randomization criteria were applied using a predefined program (http://www.randomization.com).

The inclusion criteria were: plantar heel pain diagnosed clinically and by ultrasound as plantar fasciitis, that has not responded to conservative treatment for at least six months; age between 18 and 80 years.

Exclusion criteria were: history of previous fractures or ankle and heel surgery; recurrence of previous local painful episodes; lesion of the plantar fascia on ultrasound examination; presence of pathologies that affect the function of the foot (lumbar radiculopathy, Achilles tendinitis, Morton's neuroma, etc.); chronic inflammatory conditions such as psoriasis, psoriatic arthritis, spondyloarthritis, ankylosing spondylitis, rheumatoid arthritis, chronic inflammatory bowel disease.

2.2. Treatment Protocol

Both groups received ESWT treatment delivered with an electromagnetic generator equipped with ultrasound probe (Minilith SL 1, Storz, Swiss). The patient was placed in a prone position, and the calcaneal insertion of the plantar fascia was identified under ultrasound guidance. We performed three sessions with a weekly interval. We delivered 2000 shots per session using a low/medium energy level (range between 0.01 and 0.175 mJ/mm2) depending on the patient's tolerance during treatment with a frequency of 4 Hz.

Group A patients received ESWT treatment alone, and Group B received ESWT treatment combined with a treatment cycle with a complex dietary supplement based on Methylsulfonylmethane (2.5 g), hydrolyzed collagen (1 g), L-arginine (1 g), L-lysine (500 mg), Vitamin C (500 mg), Bromelain (200 mg), Chondroitin sulfate (150 mg), Glucosamine (150 mg) [17,18], dry extracts of turmeric (100 mg), Boswellia (100 mg) and Myrrh (50 mg) (TENDISULFUR® PRO, Laborest, Italy). The supplement was administered at the dosage of one sachet twice a day for an initial period of 30 days, and then one sachet per day for an additional 60 days.

The evaluation times were T0 (recruitment), T1 (after three months) and T2 (after six months). At recruitment (T0), epidemiological (age, weight, BMI, gender, smoking), anamnesis and clinical data (mode of onset of pain, previous therapies, instrumental examinations, co-morbidities, etc.) of the patients were collected. VAS, AOFAS, Foot Function Index (FFI) evaluation scales were administered at each evaluation moment. At T1 and T2, the Roles and Maudsley Score was also administered.

As a primary endpoint, pain was quantified using the VAS scale with scores ranging from 0 (no pain) to 10 (worst imaginable pain).

As a secondary endpoint, the functional recovery was monitored using the American Foot & Ankle Score (AOFAS) with the scores ranging from 100 (no disability) to 0 (maximum disability) and the Foot Function Index (FFI) with the scores ranging from 100 (no disability) to 0 (maximum disability).

In addition, the Roles & Maudsley (R&M) scale administered only at follow-up visits allowed the monitorization of the patient's perception of improvement, with the scores ranging from 1 (excellent) to 4 (minimum).

2.3. Methods

The collected data were analyzed using “Stata MP16” software.

Continuous variables were expressed as mean±standard deviation and range, and categorical variables as proportions.

The normality of continuous variables was evaluated and a standardization model was set for those not normally distributed. Continuous variables were compared between groups using the Student t test for independent data or the Wilcoxon rank-sum test, while the ANOVA test for repeated measures was used for comparison between groups and detection times. Categorical variables were compared using the chi-square test or Fisher's exact test.

Univariate linear regression was used to evaluate the correlation between the differences in VAS, AOFAS, FFI between T2 and T0 and R&M between T1 and T2 and various determinants. Subsequently, some multivariate linear regression models were set up between the single outcome and the group variable (group B vs. group A), adjusted for age at enrollment and those determinants resulted associated in the univariate regression. The

correlation coefficients were calculated with reference to a 95% confidence interval (95% CI).

A p-value <0.05 was considered significant for all tests.

3. Results

3.1. Characteristics of the Study Population

The study sample includes 44 subjects, of which 18 (40.9%) are included in Group A, and 26 (59.1%) in Group B. Table 1 describes the characteristics of the sample.

The outcomes evaluated by detection time and group demonstrate a statistically significant difference for time for VAS, AOFAS and FFI and time-group interaction for VAS and AOFAS (Table 2). For R&M, a statistically significant difference is detected in the comparison between groups.

The comparison between groups of the outcomes, evaluated per single revelation time, is described in Table 3.

The univariate analysis between the determinants (gender, age, side, smoking, previous therapies, treatment, BMI, onset of symptoms) and the difference in VAS between T2 and T0 demonstrated a statistically significant difference for smoking (coefficient -3.6, 95% CI: -6.3 - -0.8, p: 0.012) and for BMI (coefficient 0.3, 95% CI: -0.4- -01, p: 0.007); the multivariate analysis confirmed the association with BMI (coefficient 0.21, 95% CI: 0.03-0.39, p: 0.027) and smoking (coefficient -2.60, 95% CI: -5.22 – 0.02, p: 0.051; limits of statistical significance).

Table 1. Characteristics of the sample by group (Group A vs. Group B). Statistically significant values are indicated with *

Variable	Group A (n=18)	Group B (n=26)	Total (n=44)	p-value
Female; n (%)	11 (61.1)	12 (46.2)	23 (52.3)	0.329
Age, mean±SD (range)	60.6±10.3 (38-78)	51.6±13.3 (20-73)	55.3±12.8 (20-78)	0.021 (*)
Weight, mean±SD (range)	80.0±16.6 (50-125)	78.7±12.2 (50-110)	79.2±14.0 (50-125)	0.884
Height, mean±SD (range)	164.7±7.9 (147-180)	170.6±8.7 (158-189)	168.2±8.8 (147-189)	0.027 (*)
BMI, mean±SD (range)	29.4±5.9 (20.6-48.8)	27.0±3.6 (19.2-34.8)	28.9±4.8 (19.2-48.8)	0.121
Smoking; n (%)	1 (5.6)	4 (15.4)	5 (11.4)	0.312
Onset of symptoms (week), mean±SD (range)	38.9±16.5 (15-80)	34.8±11.7 (24-52)	36.5±13.9 (15-80)	0.553
Retro-calcaneal spur; n (%)	6 (33.3)	4 (15.4)	10 (22.7)	0.162
Sub-calcaneal spur; n (%)	16 (88.9)	18 (69.2)	34 (77.3)	0.126

Table 2. Description of outcomes by group (Group A vs. Group B) and time of detection

Variable	Group A (n=18)	Group B (n=26)	Total (n=44)	p-value
VAS				
T0	7.3±1.4 (5-10)	7.4±1.4 (5-10)	7.4±1.4 (5-10)	Groups p=0.107 Times p=0.000 Time-group interaction p=0.037
T1	4.5±2.6 (0-8)	3.2±2.7 (0-8)	3.7±3.0 (0-8)	
T2	4.7±3.6 (0-10)	2.8±3.1 (0-10)	3.5±3.4 (0-10)	
AOFAS				
T0	69.9±9.3 (50-85)	61.7±14.5 (41-88)	65.1±13.1 (41-88)	Groups p=0.682 Times p=0.000 Time-group interaction p=0.002
T1	81.9±12.0 (49-100)	87.1±9.7 (70-100)	85.0±10.9 (49-100)	
T2	79.7±17.3 (48-100)	86.5±15.4 (40-100)	83.7±16.4 (40-100)	
FFI				
T0	66.2±12.2 (40-92)	66.9±10.8 (40-86)	66.6±11.3 (40-92)	Groups p=0.083 Times p=0.000 Time-group interaction p=0.054
T1	36.4±21.9 (0-71)	22.3±21.3 (0-63)	28.0±22.4 (0-71)	
T2	29.9±22.7 (0-70)	18.5±23.4 (0-74)	23.2±23.6 (0-74)	
Roles & Maudsley				
T0	-	-	-	Groups p=0.018 Times p=0.987 Time-group interaction p=0.405
T1	2.4±0.8 (1-4)	1.9±0.8 (1-4)	2.1±0.9 (1-4)	
T2	2.5±1.2 (1-4)	1.8±0.9 (1-4)	2.1±1.1 (1-4)	

Table 3. Comparison between groups of VAS, AOFAS, FFI and Roles & Maudsley

Outcome	T0	T1	T2
VAS	p-value=0.904	p-value=0.104	p-value=0.065
AOFAS	p-value=0.040	p-value=0.125	p-value=0.158
FFI	p-value=0.832	p-value=0.039	p-value=0.115
Roles & Maudsley		p-value=0.054	p-value=0.023

The univariate analysis of the determinants of the difference in AOFAS between T2 and T0 showed a statistically significant difference for groups (coefficient 15.1, 95% CI: 4.3-25.9, p = 0.007) and BMI (univariate analysis: coefficient -1.7, 95% CI: -2.8 - -0.6, p = 0.004); the multivariate analysis confirmed the association with groups (coefficient 11.1, 95% CI: -0.2-22.3, p: 0.054; limits of statistical significance) and BMI (coefficient -1.33, 95% CI: -2.5 – -0.2, p: 0.021).

The univariate analysis of the determinants of the difference in FFI between T2 and T0 showed a statistically significant difference for smoke (coefficient -29.8, 95% CI: -51.0 - -8.6, p = 0.007) and BMI (coefficient 1.6, 95% CI: 0.2-3.1, p = 0.030); the multivariate analysis only showed a statistically significant difference with smoking (coefficient -23.9, 95% CI: -45.0 - -2.7, p: 0.028).

The univariate analysis of the determinants of the difference in R&M between T1 and T2 shows a statistically significant difference for smoke (coefficient -0.9, 95% CI: -1.7 - -0.1, p = 0.033) and BMI (coefficient 0.08, 95% CI: 0.03-0.13, p = 0.002); the multivariate analysis only showed a statistically significant difference with BMI (coefficient 0.07, 95% CI: 0.02-0.13, p = 0.010).

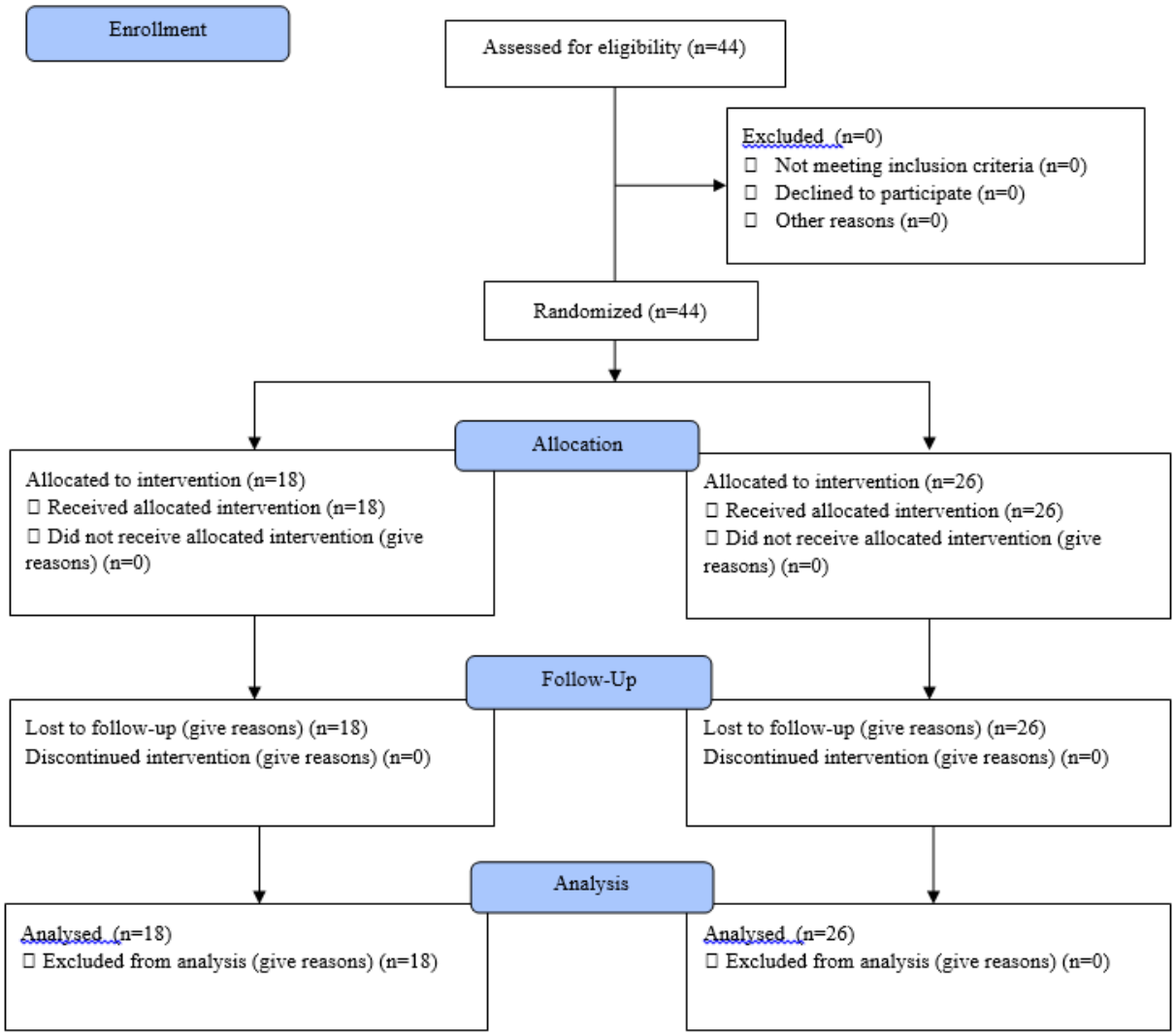

Figure 1. CONSORT 2010 Flow Diagram

4. Discussion

The most important finding of our study was that the combined effect of a tendon supplement and focused shockwaves achieved a better therapeutic response in the treatment of plantar fasciitis.

These results are consistent with the known biological effects of shock wave therapy and the components present in the supplement. Vitali et al. [19] showed on three different models of tendinopathy (epicondylitis, Achilles tendinopathy and rotator cuff) that a combined treatment of tendon supplement (Tendisulfur Forte) and ESWT is more efficient on pain at a follow-up at 60 days compared to shock wave treatment alone. Similarly, our previous study emphasized the efficacy of daily administration of a dietary supplement containing arginine, Vinitrox, collagen, methyl-sulfonyl-methane, vitamin C, and bromelain in combination with ESWT in the treatment of Achilles tendinopathy [20]. Focused shock waves promote tenocyte differentiation and collagen synthesis, reduce the production of interleukins and metalloproteases that damage tendons, trigger the release of endorphins and growth factors that play a mitogenic and anabolic role, and increase the blood flow [21]. The experiences described in the literature in recent years show a marked increase in the use of nutraceuticals, especially in the athlete population,

to reduce the pain and prevent injuries [22], in particular, based on their ability to modulate inflammation. Preclinical results are intresting, but need to be confirmed by clinical studies. The few clinical papers on the use of nutraceuticals in tendon disorders characterized by poor methodology. In these studies more supplements were administered together. This may bias the results, and the effect of each single component cannot be defined. Furthermore, the interactions between nutraceuticals and drugs, or other dietary supplements has not been evaluated, neither their effects on chronic diseases. Therefore, so far the researchers have not attributed any definitive recommendations on the use of nutraceutical supplementation in tendinopathies. Methylsulfonylmethane has an efficient anti-inflammatory, analgesic and anti-oxidant effect [23,24]. Collagen, which is an important constituent of the tendon, improves tissues' mechanical properties [23,25,26]. Chondroitin sulfate increases collagen synthesis and improves its ultrastructural organization [27]. Vitamin C is a co-enzyme of proline hydroxylase, stimulates the synthesis of procollagen, and contributes to the normal formation of type I collagen, inducing anti-inflammatory, neo-angiogenic and anti-oxidant effects [28]. Boswellia inhibits pro-inflammatory cytokines and modulates the activity of metalloproteases [29]. Turmeric has anti-oxidant activity and modulates the transcription of numerous inflammation modulators [30,31]. L-arginine and L-lysine are essential amino acids involved in the synthesis of elastin and collagen [32,33]. Myrrh inhibits the inflammatory activation of macrophages [34]. Bromelain has anti-edema, anti-oxidant and immunosuppressive effects [35].

A possible mechanism to explain our findings is nutraceuticals can therefore contribute to the healing of tendinopathies when combined with focused shock waves, in the light of synergistic biological actions. Furthermore, ESWTs could increase the bioavailability of tendon supplements thanks to the proven neo-angiogenic properties.

A limitation of this study is the absence of instrumental monitoring (ultrasound, MRI) at follow-ups. On the other hand, an in-depth examination of the effects of a supplement composed of different substances must be underlined as a strength of the research. Other limitations of the study are the lack of homogenization by age of the two groups and the presence of high BMI values, which could affect the therapeutic response of the tendons.

5. Conclusions

The results of this study demonstrate a positive therapeutic effect of the combination of focused shock wave therapy and a complex tendon supplement in the treatment of plantar fasciitis. Therefore, we believe more studies could support the effectiveness of the combination of physical therapies and supplements.

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Conflicts of Interest

The authors declare that they have no conflict of interest.

Abbreviations

The following abbreviations are used in this manuscript:

VEGF	Vascular Endothelial Growth Factor
ESWT	Extracorporeal Focused Shock Wave Therapy
RCTs	Randomized Controlled Trials
T0	TIME 0 recruitment
T1	TIME 1 (after three months)
T2	TIME 2 (after six months)
VAS	Visual Analogic Scale
AOFAS	American Foot & Ankle
FFI	Foot Function Index
R&M	Roles & Maudsley
p	p Value
ANOVA	Analysis of Variance
CI	Confidence Interval
n	Number
SD	Standard Deviation
BMI	Body Mass Index
MRI	Magnetic Resonance Imaging

References

[1] Vitali, M, Peretti, G, Mangiavini, L, "The treatment with extracorporal shock wave therapy in some of most frequently musculoskeletal pathologies," *Orthopaedic Proceedings*, 88-B: 423, 2006.

[2] Roxas, M. "Plantar fasciitis: Diagnosis and therapeutic considerations," *Altern. Med. Rev*, 10: 83-93, 2005.

[3] Hyer, CF, Vancourt R, Block A, "Evaluation of ultrasound-guided extracorporeal shock wave therapy (ESWT) in the treatment of chronic plantar fasciitis," *J. Foot Ankle Surg*, 2005, 44: 137-143.

[4] Li, S, Wang, K, Sun, H, Luo, X, Wang, P, Fang, S, Chen, H, Sun, X, "Clinical effects of extracorporeal shock-wave therapy and ultrasound-guided local corticosteroid injections for plantar fasciitis in adults: A meta-analysis of randomized controlled trials," *Medicine*, 97: e13687, 2018.

[5] Janisse, DJ, Janisse, E, "Shoe modification and the use of orthoses in the treatment of foot and ankle pathology," *J. Am. Acad. Orthop. Surg*, 16: 152-158, 2008.

[6] Nahin, RL, "Prevalence and Pharmaceutical Treatment of Plantar Fasciitis in United States Adults," *J. Pain*, 19:885-896, 2018.

[7] Benjamin, M; Kaiser, E, Milz, S, "Structure-function relationships in tendons: a review;" *J Anat*,; 212(3): 211-28, Mar 2008

[8] Lin, TW, Cardenas, L, Soslowsky, LJ, "Biomechanics of tendon injury and repair," *J Biomech*, 37(6): 865-77, Jun 2004.

[9] Coombs, R, Schaden, W, Zhou, SS, "Musculoskeletal Shockwave Therapy," *Greenwich Medical Media*, Ltd London, UK 2000.

[10] Agostino, M,C,D, Frairia, R, P, Romeo, E, Amelio, L, Berta, V, Bosco, S, Gigliotti, C, Guerra, S, Messina, L, Messuri, B, Moretti, A, Notarnicola, G, Maccagnano, S, Russo, R, Saggini, M, C, Vulpiani, P, Buselli, "Extracorporeal shockwaves as regenerative therapy in orthopedic traumatology: a narrative review from basic research to clinical practice," *J Biol Regul Homeost Agents*, 30(2): 323-32, Jun 2016.

[11] Loiacono, C,Palermi, S, Massa, B, Belviso, I, Romano, V, Di Gregorio, A, Sirico, F, Sacco, "A. Tendinopathy: Pathophysiology, Therapeutic Options, and Role of Nutraceutics. A Narrative Literature Review," *Medicina (Kaunas)*, 7; 55(8):447, Aug 2019.

[12] Bokhari, MG; Murrel, Ga. "The role of nitric oxide in tendon healing," *Journal of elbow and shoulder surgery*, 2012

[13] Aiyegbusi, AI, Duru, FI, Awelimobor, D et al. "The role of aqueous extract of pineapple fruit parts on the healing of acute crush tendon injury," Nigerian quarterly journal of hospital medicine, 2010.

[14] Shakibaei, M, Buhrmann, C, Mobasheri, "A. Anti-inflammatory and anti-catabolic effects of TENDOACTIVE on human tenocytes in vitro," *Histology and Histopathology*, 2011.

[15] Fusini, F; Bisicchia, S; Bottegoni, C; Gigante, A; Zanchini, F; Busilacchi, A, "Nutraceutical supplement in the management of tendinopathies: a systematic review," *Muscles Ligaments Tendons J*,;6(1):48-57, May 2016.

[16] Gumina, S, Passaretti, D, Gurzì, MD, Candela, V. Share, "Arginine L-alpha- ketoglutarate, methylsulfonylmethane, hydrolyzed type I collagen and bromelain in rotator cuff tear repair: a prospective randomized study," *Curr Med Res Opin*, PMID: 23043451, Oct 2012.

[17] Notarnicola, A, Maccagnano, G; Moretti, L, Pesce, V, Tafuri, S, Fiore, A, Moretti, B, "Methylsulfonylmethane and boswellic acids versus glucosamine sulfate in the treatment of knee arthritis: Randomized trial," *Int J Immunopathol Pharmacol*, 29(1): 140-146, Mar 2016.

[18] Notarnicola, A, Tafuri, S, Fusaro, L, Moretti, L, Pesce, V; Moretti, B, "The "MESACA" study: methylsulfonylmethane and boswellic acids in the treatment of gonarthrosis," *Adv Ther*, 28(10):894-906, 2011 Oct.

[19] Vitali, M, Naim Rodriguez, N, Pironti, P, Drossinos, A, Di Carlo, G, Chawla, A, Gianfranco, F, "ESWT and nutraceutical supplementation (Tendisulfur Forte) vs ESWT-only in the treatment of lateral epicondylitis, Achilles tendinopathy, and rotator cuff tendinopathy: a comparative study," *J Drug Assess*, 8(1):77-86. May 2019.

[20] Notarnicola, A, Pesce, V, Vicenti, G et al, "SWAAT study: extracorporeal shock wave therapy and arginine supplementation and other nutraceuticals for insertional achilles tendinopathy," *Adv Ther*, 29: 799-814, 2012.

[21] Visco, V, Vulpiani, M.C, Torrisi, M.R, Ferretti, A, Pavan, A, Vetrano, M, "Experimental studies on the biological effects of extracorporeal shock wave therapy on tendon models. A review of the literature," *Muscles Ligaments Tendons J*, 4(3): 357-361, 2014 Jul-Sep.

[22] Leone, L, Vetrano, M, Ranieri, D, Raffa, S, Vulpiani, M C, Ferretti, A, Torrisi, M R, Visco, V, "Extracorporeal Shock Wave Treatment (ESWT) Improves In Vitro Functional Activities of Ruptured Human Tendon-Derived Tenocytes," *PLoS One*,; 7(11): e49759, 2012.

[23] Loiacono, C, Palermi, S, Massa, B, Belviso, I, Romano, V, Di Gregorio, A, Sirico, F, Sacco, A.M, "Tendinopathy: Pathophysiology, Therapeutic Options, and Role of Nutraceutics. A Narrative Literature Review," *Medicina (Kaunas)*, 55(8): 447, Aug 2019.

[24] Butawan, M, Benjamin, R.L, Bloomer, R.J, "Methylsulfonylmethane: Applications and Safety of a Novel Dietary Supplement," *Nutrients*, 9(3): 290, Mar 2017

[25] Lugo, JP; Saiyed, ZM; Lane, NE, "Efficacy and tolerability of an undenatured type II collagen supplement in modulating knee osteoarthritis symptoms: a multicenter randomized, double-blind, placebo-controlled study," *Nutr J*, 15: 14., Jan 2016.

[26] Crowley, DC; Lau, FC; Sharma, P et al, "Safety and efficacy of undenatured type II collagen in the treatment of osteoarthritis of the knee: a clinical trial," *Int J Med Sci*, 6(6): 312-21, 2009.

[27] Oliva, F, Gallorini, M, Antonetti Lamorgese Passeri, C, Gissi, C, Ricci, A, Cataldi, A, Colosimo, A, Berardi, A.C, "Conjugation with Methylsulfonylmethane Improves Hyaluronic Acid Anti-Inflammatory Activity in a Hydrogen Peroxide-Exposed Tenocyte Culture In Vitro Model," *Int J Mol Sci*, 21(21): 7956, Oct 2020.

[28] Du Souich, P, García, A.G, Vergés, J, Montell, E, "Immunomodulatory and anti-inflammatory effects of chondroitin sulphate," *J Cell Mol Med*, 13(8a): 1451-1463, Aug 2009.

[29] DePhillipo, N.N; Aman, Z S; Mitchell, I; Kennedy, J P; Begley, G M; LaPrade, F, "Efficacy of Vitamin C Supplementation on Collagen Synthesis and Oxidative Stress After Musculoskeletal Injuries: A Systematic Review," *Orthop J Sports Med*, 6(10): 2325967118804544, Oct 2018.

[30] Merolla, G, Dellabiancia, F, Ingardia, A, Paladini, P, Porcellini, G, "Co-analgesic therapy for arthroscopic supraspinatus tendon repair pain using a dietary supplement containing Boswellia serrata and Curcuma longa: a prospective randomized placebo-controlled study," *Musculoskelet Surg*, 99 Suppl 1():S43-52, Sep 2015.

[31] Peddada, K V, Peddada, K V, Surendra, K S, Mishra, A, Verma, V, "Role of Curcumin in Common Musculoskeletal Disorders: a Review of Current Laboratory Translational, and Clinical Data," *Orthop Surg*, 7(3): 222–231, Aug 2015.

[32] Mollazadeh, H, Cicero, AFG, Blesso, CN, Pirro, M, Majeed, M, Sahebkar, A, "Immune modulation by curcumin: The role of interleukin-10," *Crit Rev Food Sci Nutr*, 59(1): 89-101. 2019.

[33] Collier, TA; Nash, A; Birch, H L; de Leeuw, N H, "Intra-molecular lysine-arginine derived advanced glycation end-product cross-linking in Type I collagen: A molecular dynamics simulation study," *Biophys Chem*, 218: 42-46, Nov 2016.

[34] Molinari, C, Morsanuto, V, Polli, S, Uberti, F, "Cooperative Effects of Q10, Vitamin D3, and L-Arginine on Cardiac and Endothelial Cells," *J Vasc Res*, 55(1):47-60, 2018.

[35] Onken, JE, Greer, PK, Calingaert, B, Hale, LP, "Bromelain treatment decreases secretion of pro-inflammatory cytokines and chemokines by colon biopsies in vitro," *Clin Immunol*, 126(3):345-52, Mar 2008.