Clinical Research on Foot & Ankle
ISSN: 2329-910X
Vashishtha V, et al. Clin Res Foot Ankle 2021, 9:10
Research Article Open Access

A Placebo-Controlled, Double Blind Study to Evaluate the Efficacy and Safety of a Combination of Mucopolysaccharides, Collagen Type-I and Vitamin C in Patients with Tendinopathy

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Abstract

Background: Tendinopathy is the most common disorder of tendons. The aim of present study was to evaluate the efficacy and safety of combination of mucopolysaccharides, collagen type-I and vitamin C in patients with tendinopathy.

Methods: This placebo-controlled, double blind study was conducted in 100 patients (active-50, placebo-50); amongst them 50 patients each had Achilles tendinopathy and plantar fasciitis respectively. Patients received either active combination therapy or placebo capsules which was administered twice daily for 90 days. Rescue analgesic tablets were also dispensed for use as required. Patients were followed up on day 15, 30, 60 and 90. Efficacy assessments included 0-100 Visual Analogue Scale (VAS) score for pain on activity and at rest, VISA-A questionnaire and AOFAS scale score, rescue analgesic use and overall assessment of treatment by patients. Safety was based on reported Adverse Events (AEs).

Results: 97/100 patients completed the study. The scores of VAS for pain, VISA-A and AOFAS were comparable at baseline ($P>0.05$). There was gradual decline in VAS scores for pain and gradual improvement in VISA-A and AOFAS scores with change from baseline being significantly higher in active group at the end of study ($P<0.05$). The usage of rescue analgesic was significantly lesser for day 31-60 and day 61-90 in the active group ($P<0.01$). Trend on overall assessment also favored active drug. No treatment emergent AEs reported in the study.

Conclusion: The combination of mucopolysaccharides, collagen type-I and vitamin C can be considered a safe and effective supportive therapy in patients with tendinopathy.

Keywords

Achilles tendinopathy; Collagen type-I; Mucopolysaccharides; Plantar fasciitis; Tendinopathy; Vitamin C

Introduction

Tendons are specialized tissues that connect muscles to bones and are involved in joint movement [1]. Tendinopathy is a broad term used to describe multifaceted pathology of tendon (s) which is characterized by pain on activity, localized tenderness and swelling, and reduced function and exercise tolerance [1,2]. It not only hampers the quality of life of the patients but is also associated with a significant socioeconomic burden and loss of work hours [3].

Tendinopathy is the most common disorder of tendons 1 and it accounts for around 30% consultations related to musculoskeletal disorders [3-5]. It affects a significant proportion of athletes and individuals involved in repetitive work due to overuse conditions [1]. It has been estimated to account for 30%-50% sport related injuries [6]. The evidence suggests that in addition to athletes, the general and elderly populations are also affected by inflammatory or degenerative tendinopathies [4]. The microscopic characteristics of tendinopathy include structural disorganization of the collagen tissue, degeneration of the extracellular and neovascularization [6].

Incidence of tendinopathies has increased over the recent years owing to increased involvement of individuals in sporting activities, increased life expectancy, systemic disorders, certain drug therapies adversely affecting the tendons and other environmental and dietary factors [3,4]. Studies have also indicated a causal link between tendinopathy and metabolic disorders such as hypercholesterolemia and diabetes mellitus [7-10]. Tendinopathy can affect almost any tendon in the body; however, some tendons are more likely to be affected than others [1,4]. Achilles tendinopathy and plantar fasciitis are one of the common forms of tendinopathy encountered in clinical practice [1].

The mainstay of management of tendinopathy consist of pain management, physical exercises and prevention of recurrence. Surgical approach is usually considered when conservative therapy has failed to achieve desired results. Most of the treatment options do not correct the structural abnormality of tendon and therefore, despite the use of conventional therapies, structural and mechanical properties of the affected tendon may not match with the healthy tendon which makes the tendon weaker and susceptible to further injury and carries the risk of long term disability [3]. One of the important reasons of limited effective treatment options of tendinopathy is

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Received: October 13, 2021**; Accepted:** October 27, 2021**; Published:** November 3, 2021.

Citation: Vashishtha V, Pingat A, Patel C, Madini M, Pawar R, et al. (2021) A Placebo-Controlled, Double Blind Study to Evaluate the Efficacy and Safety of a Nutritional Supplement Containing Mucopolysaccharides, Collagen Type-I and Vitamin C In Patients with Tendinopathy. Clin Res Foot Ankle 9: 325.

poor understanding regarding its pathogenesis [1]. Hence, there remains a constant interest in alternate therapies which can support and enhance physiological healing leading to development of physiologically normal tendons.

The supportive therapy with oral supplements containing nutraceuticals has been proposed in recent past for maintenance of physiological turnover of tendon tissue and prevention of its degeneration. These supplements may not only preserve but even help in repairing the affected tendons [4]. Various supplements used in clinical practice with the above concept of "teno-protection" include mucopolysaccharides, type I collagen, vitamin C, glucosamine and chondroitin sulphates, boswellic acid, curcumin, methylsulfonylmethane and bromelain [3,4]. Based on the above rationale, the current study was conducted with an aim to evaluate the efficacy and safety of a nutritional supplement containing mucopolysaccharides, collagen type-I and vitamin C in patients with Achilles tendinopathy and plantar fasciitis.

Methods

This was a prospective, randomized, double blind, two arm, placebo controlled, parallel, multicenter clinical study. This study was conducted from October, 2020 to February, 2021 at 4 sites in India in compliance with Ethical Guidelines for Biomedical Research on Human Participants, Indian Council of Medical Research. The approvals from registered Institutional Ethics Committees were obtained by respective investigators before initiation of enrollment at the respective sites. Written informed consent was obtained from all the participants before performing any screening related activity.

Patients of both the genders aged 18 to 70 years with clinical diagnosis of Achilles tendinopathy or plantar fasciitis, having pain on activity of ≥ 40 on 0-100 Visual Analogue Scale (VAS) at the baseline (0 refers to no pain and 100 refers to worst pain) and willing to comply with the protocol requirements were considered for enrollment in the study. Patients with history of hypersensitivity to any component of the study drug; patients who have used systemic steroids within past 3 months or non-steroidal anti-inflammatory drugs within past 3 days; patients with recent history of administration of intralesional platelet rich plasma or other medications that may cause tendinopathy (such as fluoroquinolones), or history of local therapy for management of tendinopathy; patients with suspected musculoskeletal disorders (spondyloarthropathy, gout, rheumatoid arthritis, sarcoidosis), suspected musculoskeletal injuries (insertional disorders, tendon rupture), arthritis, neurological disorder, systemic inflammatory disorder, gastrointestinal ulcer/bleeding or uncontrolled diabetes; patients with continuing history of alcohol or drug abuse; patients who have participated in other clinical trial within past 3 months; pregnant and lactating females and females of child bearing age not using acceptable contraceptive measures were excluded.

Eligible patients were randomized in 1:1 allocation ratio to receive either the active drug (T Heal capsules) or matching placebo according to the centralized computer generated randomization plan. Both the active drug and placebo were manufactured by M/s. Alkem Laboratories Ltd following the good manufacturing practices. The active drug contained mucopolysaccharides 220 mg, collagen type-I 40 mg and vitamin C 20 mg. All the physical characteristics of active drug and placebo were similar to maintain the double blinding. The study sites were provided with patient kits bearing unique randomization number without revealing the study medication contained therein. The sites were also provided sealed blinding codes for each patient kit; however, unblinding was not required for any patient in the study.

There were a total of 5 visits in the study. After enrollment (day 0), patients were followed up with scheduled visits on day 15, 30, 60 and 90. Patients were dispensed monthly supplies of allocated study medication (active drug or placebo) at baseline and on day 30 and 60. Patients were instructed to take one capsule twice daily orally, swallowed as a whole with water around the same time daily throughout the study duration. Patients were also dispensed analgesic tablets at baseline and on day 30 and 60 for use as rescue medication as and when required. Patients were instructed to bring leftover study medication and rescue medication on subsequent visits to evaluate the compliance to study medication and usage of rescue medication respectively using the pill count method.

During each visit, a routine clinical examination was performed and patients were enquired for any concomitant disorders and medications. Patients were also asked to rate their pain score on activity and at rest on 0-100 VAS at each visit. Further, the score of Victorian Institute of Sport Assessment Achilles (VISA-A) questionnaire was evaluated for patients with Achilles tendinopathy and score of American Orthopaedic Foot and Ankle Society-Ankle Hindfoot (AOFAS) scale was evaluated for patients with patients with plantar fasciitis at each visit. VISA-A is a valid, reliable, and patient self-administered disease specific questionnaire to assess the severity of Achilles tendinopathy. This questionnaire consists of 8 questions that measures three domains of pain, function in daily living and sporting activity. The total score ranges from 0-100 where lower score reflects a higher disease activity [11,12]. AOFAS scale is among the most commonly used instruments for measuring the outcome of treatment in patients who sustained a complex ankle or hindfoot disorder. It combines both subjective and objective information. Patients are asked to report their pain and function while physician assesses alignment of the foot. Like VISA-A questionnaire, the total score of this scale ranges from 0-100 where lower score reflects a higher disease activity [13,14]. At the end of study, patients were also asked to rate their overall assessment of treatment based on the change from baseline in the disease condition on a 7 point scale as follows: Very much improved, much improved, minimally improved, no change, minimally worse, much worse and very much worse. The efficacy evaluations were performed on the index leg. If both legs were affected, the one with more severe disease was considered as the index leg. If both legs had similar disease activity then right leg was considered as the index leg.

The primary efficacy variable was change from baseline in VAS score for pain on activity at various time points during the treatment period. The secondary efficacy variables were change from baseline in VAS score for pain at rest, change from baseline in VISA-A questionnaire score in patients with Achilles tendinopathy and change from baseline in AOFAS scale score in patients with plantar fasciitis at various time points during the treatment period; mean number of analgesic tablets consumed during the treatment period and overall assessment of treatment by the patients at the end of the study. The safety variables were AEs and serious AEs, if any, reported during the study. The intensity (mild, moderate or severe) and causal relationship (related or not related) of AEs with the study medication was evaluated by the investigators.

A sample size of 100 patients was considered for this study with equal allocation in both the study groups (active drug-50, placebo-50) for exploratory purpose. No assumptions were made to determine the sample size for this study. Amongst the 100 enrolled subjects, 50 patients each had Achilles tendinopathy and plantar fasciitis.

The continuous data has been presented as mean ± SD while the categorical data has been presented as number (proportion). The continuous data such as change in VAS score was compared between the groups using unpaired t test while categorical data was compared using Chi square test. The change from baseline in VAS, VISA-A questionnaire and AOFAS

scale over the treatment period within the study groups was assessed using repeated measure ANOVA. P<0.05 was considered as statistically significant. The last observation carried forward method was used to impute the missing data of discontinued subjects.

Ethics

Approvals from the registered Institutional Ethics Committees of respective sites were obtained.

Results

A total of 100 patients were enrolled in the study out of which 97 subjects completed the study (Figure 1). All the demographic parameters and baseline characteristics of the disease condition such as VAS scores for pain on activity and rest, VISA-A score and AOFAS score at the baseline were comparable between the study groups (P>0.05) (Table 1).

Parameter		Active	Placebo	P value
		N=50	N=50	
Age (years)		49.2 ± 10.4	47.5 ± 12.8	0.46
	Male	26 (52.0%)	21 (42.0%)	
Gender*	Female	24 (48.0%)	29 (58.0%)	0.42
Height (cm)		160.9 ± 7.0	159.7 ± 6.9	0.39
Weight (kg)		62.6 ± 7.1	61.6 ± 9.6	0.56
	Activity	64.7 ± 4.8	62.6 ± 5.8	0.06
VAS score*	Rest	35.7 ± 3.3	35.3 ± 2.8	0.49
		N=25	N=25	
VISA-A score#		40.3 ± 4.9	40.8 ± 4.3	0.71
AOFAS score$		60.6 ± 14.8	56.2 ± 12.7	0.27
Data presented as mean ± SD unless specified *Data presented as n (%) #Evaluated in patients with Achilles tendinopathy $Evaluated in patients with plantar fasciitis				

Table 1: Demographic characteristics of enrolled subjects. VAS-Visual analogue scale; VISA-A-Victorian Institute of Sport Assessment-Achilles questionnaire; AOFAS-American Orthopedic Foot and Ankle Society-Ankle-Hindfoot scale

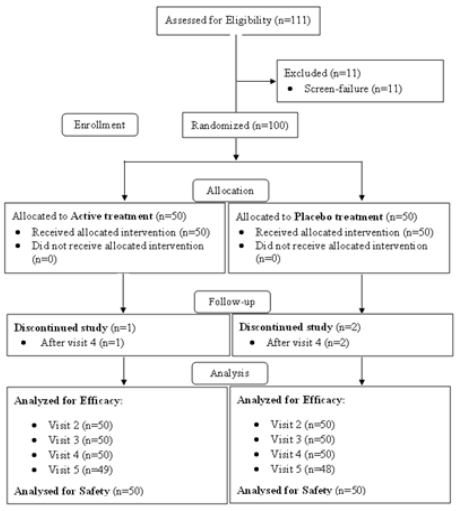

Figure 1: Study flow chart

Efficacy

The mean (SD) VAS score for pain on activity gradually decreased from 64.7 (4.8) at the baseline to 19.0 (8.6) at the end of the study in the active group and from 62.6 (5.8) at the baseline to 30.5 (8.3) at the end of the study in the placebo group. The change from baseline in VAS score for pain on activity was significantly higher in the active group as compared to the placebo group at all the follow up visits during the treatment period (Figure 2). Likewise, the mean VAS score for pain at rest gradually decreased from 35.7 (3.3) at the baseline to 11.0 (6.3) at the end of the study in the active group and from 35.3 (2.8) at the baseline to 19.2 (4.8) at the end of the study in the placebo group. The change from baseline in VAS score for pain at rest was also significantly higher in the active group as compared to the placebo group at all the follow up visits during the treatment period (Figure 3).

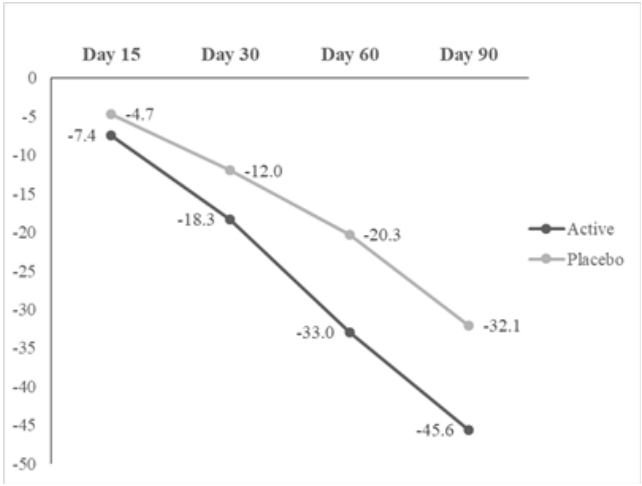

Figure 2: Change from baseline in VAS score during activity at various timepoints during the study. P <0.0001 for inter-group comparison at all timepoints.

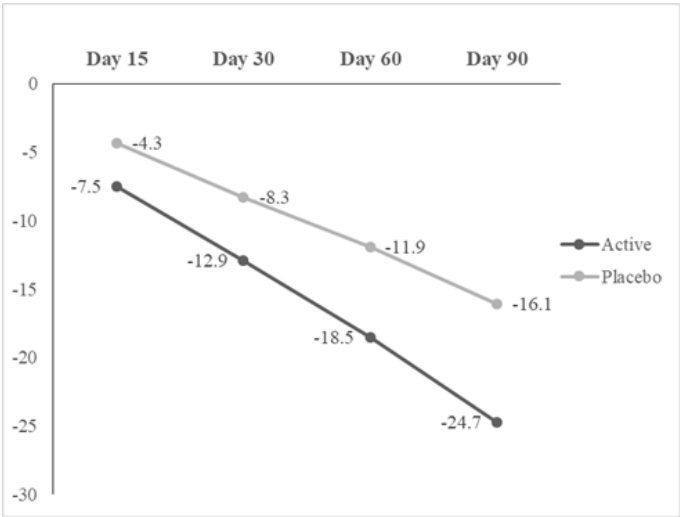

Figure 3: Change from baseline in VAS score at rest at various timepoints during the study. P <0.0001 for inter-group comparison at all timepoints.

The mean VISA-A score in patients with Achilles tendinopathy gradually improved from 40.3 (4.9) at the baseline to 82.6 (12.8) at the end of the study in the active group and from 40.8 (4.3) at the baseline to 69.5 (10.0) at the end of the study in the placebo group. The change from baseline in

VISA-A score was significantly higher in the active group as compared to the placebo group starting from day 30 through the end of the study (Figure 4).

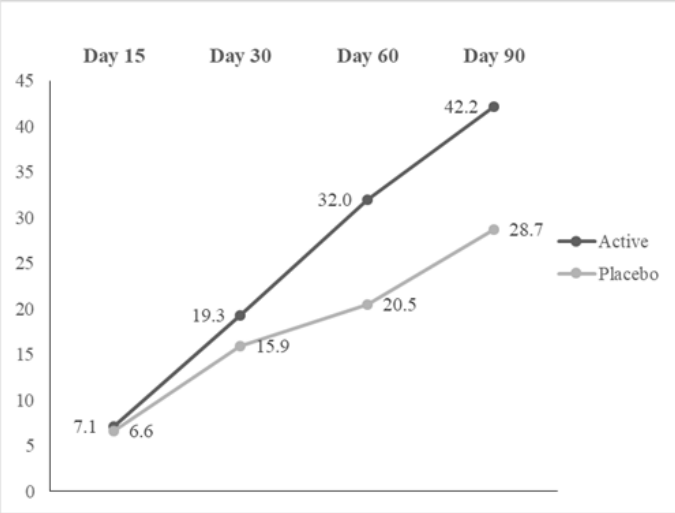

Figure 4: Change from baseline in VISA-A score in patents with Achilles tendinopathy at various timepoints during the study. P=0.59, P=0.04 and P<0.0001 for inter-group comparison at day 15, day 30 and at both day 60 & 90 timepoints respectively.

The mean AOFAS score in patients with plantar fasciitis gradually improved from 60.6 (14.8) at the baseline to 90.7 (8.6) at the end of the study in the active group and from 56.2 (12.7) at the baseline to 72.4 (6.7) at the end of the study in the placebo group. The change from baseline in AOFAS score was significantly higher in the active group as compared to the placebo group at day 60 and at the end of the study (Figure 5).

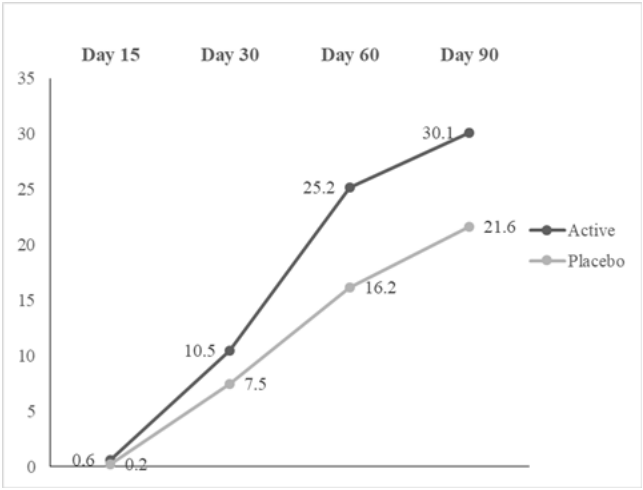

Figure 5: Change from baseline in AOFAS score in patents with plantar fasciitis at various timepoints during the study. P=0.13, P=0.23, P=0.0006 and P=0.0015 for inter-group comparison at day 15, day 30, day 60 and day 90 timepoints respectively.

The mean number of rescue analgesic tablets consumed between day 1-30, day 31-60 and day 61-90 in the treatment period were 24.1 (2.1), 14.4 (2.8) and 8.9 (1.1) in the active group and 24.6 (1.9), 15.9 (1.0) and 12.3 (1.1) in the placebo group respectively. The usage of rescue analgesic was comparable between the groups for day 1-30 while it was significantly lower in the active drug as compared to placebo group for day 31-60 and day 61-90 (P<0.05).

Overall assessment of treatment by the patients at the end of the study was comparable between the study group (Table 2); however, a relatively higher number of patients in the active group, 37 (75.5%) had responded as 'very much improved' or 'much improved' as compared to placebo group, 26 (54.2%). No patient reported worsening of disease condition.

Assessment grade	Active (N=49)	Placebo (N=48)	P value
Very much improved	17 (34.7%)	11 (22.9%)	0.14
Much improved	20 (40.8%)	15 (31.3%)	
Minimally improved	11 (22.4%)	18 (37.5%)	
No change	1 (2.0%)	4 (8.3%)	
Data presented as n (%)			

Table 2: Overall assessment of treatment by the patients at end of the study

Safety

There were a total of 6 AEs reported by 6 patients in this study; 4 AEs were reported in active group and 2 AEs were reported in placebo group. In the active group, 2 patients had reported diarrhoea while 1 patient each had reported gastritis and headache. In the reference group, one patient each had reported gastritis and headache. None of the patients discontinued the study due to AEs. All the AEs were mild in intensity and were considered not related to study medication by the investigators. All the AEs resolved within few days of their occurrence. Three patients required supportive medications for resolution of AEs; 2 patients having gastritis were given pantoprazole and 1 patient in the active group having diarrhoea was given lactic acid bacillus supplement. No severe or serious AE was reported in any patient in the study. No clinical significant changes were reported in vitals in any patient during the study.

Discussion

This study was conducted in patients with Achilles tendinopathy and plantar fasciitis considering them as representative population for tendinopathy. The results of this study indicate that the oral supplementation with mucopolysaccharides, collagen type-I and vitamin C resulted in a better and faster resolution in pain at the affected site and it also lead to a better functional improvement in disease condition as compared to placebo. The patients who had received the supplement also reported a lesser consumption of analgesics. The trend also highlighted a better improvement in the underlying disease condition with the active drug as compared to placebo based on the patients' self-assessment of treatment response. The therapy with supplement was also found very well tolerated throughout the study.

The individual components of active drug used in this study are known to contribute to various physiological effects of tendons. Mucopolysaccharides also known as glycosaminoglycans is an essential component of extracellular matrix; it holds the tendon fibers together and helps in providing flexibility, stretching and bending properties as well as resilience. Collagen is the major extracellular protein in tendon and it contributes to its mechanical strength. Vitamin C is necessary for synthesis of collagen fibers and several glycoproteins. It also increases angiogenesis and maturation of collagen type-III to type-I fibers. The anti-inflammatory and antioxidant properties of vitamin C further aid in healing of affected tendon [3].

Beneficial effects of oral supplementation with mucopolysaccharides,

collagen type-I and vitamin C have also been reported in patients with various forms of tendinopathies as well as in animal models in in-vitro study [6,15-17]. In a single arm exploratory study conducted by Arquer et al. in patients with Achilles tendinopathy, patellar tendinopathy and tennis elbow, daily supplementation with mucopolysaccharides, collagen type-I and vitamin C resulted in a significant reduction in pain on activity and at rest both at day 30 and day 90 as compared to the baseline. A symptomatic and functional improvement was also reported on evaluation of disease specific questionnaires (VISA-A, VISA-P and PRTEE). Further, 10%-20% reduction in the thickness of affected tendons as compared to the baseline was also reported with supplement therapy when evaluated using ultrasound [6]. In another placebo-controlled study conducted by Binh et al. in patients with tendinopathy of Achilles, supraspinatus, lateral epicondyle or plantar fasciitis, daily supplementation with mucopolysaccharides, collagen type-I and vitamin C also resulted in a better reduction in pain and better resolution of symptoms (redness, swelling and burn) as compared to placebo. According to ultrasound assessment, no patient who had received the supplement had tendinopathy at the end of 90 days therapy [15]. The effectiveness of mucopolysaccharides, collagen type-I and vitamin C as a nutritional supplement was also evaluated in another study conducted by [16]. in patients with epicondylitis, supraspinous tendinopathy, Achilles tendinopathy and plantar fasciitis. In that study, the patients who received nutritional supplement over and above rehabilitation sessions had a higher pain reduction and a better functional improvement as per physiotherapist assessment as compared to those who attended rehabilitation sessions only [16]. Thus, the efficacy results reported in this study can be considered in consonance with the results of previous studies as highlighted above.

No safety concern was reported in this study and none of patients had reported any treatment emergent AE. Therefore, daily supplementation with mucopolysaccharides, collagen type-I and vitamin C can be considered safe in patients with tendinopathies.

This study was also associated with several limitations which needs mention: Firstly, this study was conducted in two subsets of tendinopathy involving lower extremity, which may limit applicability of results of this study to tendinopathies involving other body regions. Secondly, this study was conducted in a smaller number of patients. Although this smaller sample size was found appropriate to draw statistical conclusion for most of the efficacy variables, it may still be limited to observe any safety signals. Thirdly, there was a limited follow up of 3 months in the study. Since the active drug is a nutraceutical, patients with tendinopathies specifically those having chronic condition may tend to consume the supplements for even longer durations. Lastly, the structural evolution of the affected tendon over the course of therapy using radiological investigations such as ultrasound was not performed. Further large long term studies involving diverse subsets of patients with tendinopathies may be warranted to specifically answer one or more of the above highlighted limitations.

Conclusion

Overall, this study indicate that in patients with tendinopathy, the combination of mucopolysaccharides, collagen type-I and vitamin C provides a better symptomatic and functional improvement compared to placebo. The beneficial effects of this supportive therapy could be attributed to an improved physiological healing of tendons. This combination can be considered as a safe and effective supportive therapy in the patients with tendinopathy.

Funding

The study was supported by Alkem Laboratories Limited, Mumbai

Conflict of Interest

Vikalp Vashishtha, Amit Pingat, Chirag Patelx, Manoj Madini declare no conflict of interest. Roshan Pawar, Abhijit Trailokya, Akhilesh Sharma are employees of Alkem Laboratories Limited.

Acknowledgement

The Authors are very thankful and honored to publish this article in the respective Journal and are also very great full to the reviewers for their positive response to this article publication.

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