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Curcuminoids and boswellia serrata extracts combination decreases tendinopathy symptoms: findings from an open-label post-observational study

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Abstract

Background. To investigate the effects of one-month treatment in addition to standard care with a food supplement containing both Curcuma longa and Boswellia serrata extracts on tendinopathy symptoms.

Method. This open-label, non-controlled, post-observational study included 670 patients suffering from tendinopathy recruited at different sites by Belgian general practitioners. Patients received a medical prescription for one-month treatment with two tablets twice a day of a pharmaceutical grade food supplement containing both Curcuma Longa and Boswellia serrata extracts. Pain and functional limitation were evaluated using a visual analog scale at the inclusion and one-month treatment later. Patient satisfaction, concomitant drugs intake and side effects were also recorded.

Results. After one-month treatment, pain and functional limitation were significantly improved whatever the cause of tendinopathy, its localization, and the duration of symptoms. The pain score decreased from 6.16 ± 1.53 to 2.98 ± 1.64 ($p<0.0001$), yielding a drop of 51.6% and the functional limitation score fell after one-month treatment from 5.96 ± 1.73 to 2.88 ± 1.67 ($p <0.0001$) corresponding to a drop of 51.6%. The percentage of patients taking at least one concomitant treatment at the end of the treatment period had decreased from 81.3% to 61.8% ($p<0.0001$). Only 43 (6.5%) patients reported side effects. No severe adverse effects related to the product were reported.

Conclusion. The combination of Curcuma Longa and Boswellia serrata extracts improves symptoms in patients suffering of tendinopathy and shows a good safety. Although its effect will have to be confirmed in randomized controlled trials, it can be considered as a helpful support of standard symptomatic treatments for tendinopathies.

Keywords: tendinopathy, tendon, curcumin, boswellic acids, clinical study.

Running title: Curcuminoids and boswellia serrata to treat tendinopathy

Highlights:

- Tendinopathy is a common disease representing 30% of all consultations with a general practitioner for musculoskeletal disorders.
- The combination of Curcuminoids and Boswellia serrata extracts are efficient on tendinopathy symptoms in support of standard symptomatic treatments.
- The combination of Curcuminoids and Boswellia Serrata extract is safe and can be administrated for at least one month in addition of analgesic and non-steroidal anti-inflammatory drugs

Introduction

Tendinopathy is a frequent reason for consultations with a general practitioner for musculoskeletal disorders (1). The blanket term “tendinopathy” is used to describe a broad spectrum of non-rupture primary or secondary, acute or chronically degenerative tendon pathologies, which are associated with prolonged pain, functional limitation, swelling, and severely impair performance and occupational capacity (2). The pathophysiology can be viewed on a continuum proceeding divided in three phase (i) an early reactive tendinopathy (non-inflammatory proliferative response in cells and matrix) in response to acute overload or trauma, (ii) failed healing response and disrepair of the Extracellular Matrix (ECM) and finally, (iii) terminal degeneration and dysregulation of healing resulting in irreversible stage of pathology showing major structural and compositional changes, cell death, tissue breakdown and loss of function with predisposition of the tendon to further injury and rupture (3,4). Inflammation may be present, especially in the early phases, when "early tendinopathy" may not be clinically evident (4). However, in chronic prolonged tendinopathy it has been difficult to detect any biochemical markers of inflammation (5). To control early inflammation is a key objective in the management of tendinopathy.

In general, tendinopathies result from acute traumatic load, repetitive mechanical traumas or overuse beyond the capacity of the affected tendon. Besides mechanical risks, which are seen as key initial triggers for tendinopathy, multiple intrinsic individual factors seem to have a relevant impact on tendinopathy (6). Thus, age, gender, body weight and height, genetics, hormonal background (e.g. menopause), metabolic disorders (e.g. obesity, hypercholesterolemia, diabetes

mellitus, adiposity, hyperlipidemia and chronic gouty arthritis) and prior tendon injuries are ranked to influence the biological aspect of tendon pathogenesis by reducing the capability of the tendon to tolerate load and by modulating repair responses (7). Finally, tendon disorders can be triggered by several extrinsic, environmental factors, which are likely to affect the stress on the tendon tissue from the outside (8). This includes active daily life and physically demanding workplace, poor nutrition, smoking, alcohol consumption, environmental factors (e.g. cold weather and foot wear) and pharmacological agents (e.g. fluoroquinolone and quinolone antibiotics, corticosteroids, aromatase inhibitors and statins) (9, 10).

The mainstay of first-line management of early tendinopathies is conservative treatment, which comprises modification of activity, relative rest, pain relief using non-steroidal anti-inflammatory drugs (NSAIDs), as well as corticosteroid injections and cryotherapy (11). The use of corticosteroids or NSAIDs for inflammatory suppression and pain relief is controversial based on the high risk of spontaneous tendon ruptures after local or even systemic drug delivery. The traditional physiotherapy in combination with myofascial therapy, ultrasound, ionophoresis and phonophoresis and acupuncture yield clinically good results as long as no major structural damage can be observed. Non-operative strategies also include ultrasound treatment and shock wave therapy, eccentric exercises and stretching (11). They are applied in order to promote structural remodeling and repair. Many promises are given to biological therapies by platelet rich plasma (PRP), antibody therapy (e.g., Interleukin (IL)-17), IL-1β antagonist and Bone Matrix Protein (BMP) or autologous tenocyte implantation (Ortho-ATI) (12,13,14).

Until today, none of the therapeutic options offers satisfactory long-term solutions, meaning that repaired tendons do not regain their complete strength and

functionality. Food supplements are common support therapy for the management of tendinopathy Among them, oral supplements of glucosamine and chondroitin sulphate (GlcN-CS), vitamin C (vit C), hydrolyzed type 1 collagen (Col 1), L-arginine alpha-keto-glutarate (AAKG), curcumin, boswellic acids, methylsulfonylmethane (MSM), and bromelain were already studied on patient with tendinopathy (15). Recently, one particular attention was focused on Curcuma longa and Boswellia serrata extracts (CBE). The efficacy and safety of these extracts have already been established in several clinical trials and are known to have potent anti-inflammatory and analgesic effects in chronic conditions like osteoarthritis. Curcumin (diferuloylmethane) is the principal curcuminoid extracted from the Curcuma longa root and known as a powerful antioxidant. The boswellic acids, the main active ingredients of Boswellia serrata gum are known to inhibit the 5-lipooxygenase (LOX) pathway, which is a primary source of pro-inflammatory leukotrienes (16). Curcumin and boswellic acid also have inhibitory effects on nuclear factor κB (NF-κB) signaling pathway and its gene products, some of which are directly involved in the inflammatory processes and connective tissue extracellular matrix degradation (17,18). Both Curcuma longa and Boswellia formulations have been shown to counteract decreases in glycosaminoglycan levels and impede the secretion and activity of Matrix MetalloProteinases (MMPs), which could potentially forestall further degradation of connective tissue (19,20). In summary, many in vitro studies suggest that Curcuma longa and Boswellia serrata could provide a therapeutic benefit that extends beyond symptom relief to disease modification. Two recent meta-analyses evaluating a large number of dietary supplements ranked Curcuma longa and Boswellia serrata among the most effective compounds for pain reduction in OA at short-term although the quality of evidence was low (21,22). Altogether, these elements give a good rationale

to combine Curcuma longa and Boswellia serrata to relief pain and inflammation in tendinopathy.

This clinical study purposed to explore in a real-life setting the effects of a combination of Curcuma longa and Boswellia serrata extracts (CBE) on the algofunctional status of a large sample of patients suffering of tendinopathy. To the best of our knowledge, it is the first clinical trial investigating this formulation in patient suffering from tendinopathy.

Materials and Methods

Study design

This is a non-controlled, non-randomized post-observational clinical study based on a random sample of Belgian General Practitioners (GP) and dealing with patients with tendinopathy. For each GP, patients were recruited sequentially and not selectively. Patients were evaluated at study entry (baseline) and after one-month treatment with CBE (Flexofytol PLUS®, Tilman SA, Baillonville, Belgium) as prescribed by their physician in addition to the standard treatment. Patients had to pay for the CBE cure. All demographic patient characteristics and clinical outcomes were collated on a paper "case report form (CRF)" by the physician. According to the Belgian law of 7 May 2004 (Art.3§2,http://www.ejustice.just.fgov.be/cgi_loi/change_lg.pl?language=fr&la=F&cn=2004050732&table_name=loi) on human experiments, seeking approval by an ethical committee for a post-hoc observational study of data collected from the records of general practitioners (GPs) was not required. Moreover, the dietary supplement

taken in accordance with good medical practice, without patient's assignment to a given therapeutic strategy, as the decision to take the product, already on the market and available without prescription in Belgium, was not related to the study and did not require additional diagnostic or monitoring procedures.

Population

The study involved 670 patients followed by their GP between 8 October 2018 and 30 October 2019. All the patients suffered from tendinopathy. A total of 122 GPs contributed to the recruitment of patients (5.5 patients per GP).

Variables

For each patient the following variables were collected at inclusion and one month after treatment: demographic data, location, cause and history of tendinopathy, type of pain ("at rest", "when moving", or "all the time"), analog visual scale (VAS) of pain experienced during the last 48 hours, the pain-related limitation in usual movements (functional limitation) evaluated with a VAS (0 = no limitation to 10 = extreme limitation), treatment history and treatment used during the follow-up. Patient satisfaction was assessed on a 5-point grid (from "very unsatisfied" to "very satisfied"). The occurrence of adverse effects was specified by the patient and noted by the physician.

Treatment

Each patient received one-month treatment with CBE. The posology prescribed by the physician was 2 caps at breakfast and 2 caps at dinner for one month. The tested CBE (Flexofytol® PLUS) was a pharmaceutical grade food supplement which has received approval from Belgian competent authorities (NUT/PL31/145; Federal Public Service, Health, Food chain safety and environment) and commercialized by Tilman SA (Baillonville, Belgium). Each capsule contained 89 mg of bio-optimized turmeric rhizome extract (Curcuma longa L.) containing 72 mg of curcumin and 120 mg of boswellia serrata extract containing 78 mg boswellic acids. These doses were demonstrated to be efficient in osteoarthritis pain (23,24). For rescue analgesia, patients were allowed to maintain their treatments as long as necessary, included the use of paracetamol and NSAIDs (oral or local).

Statistical analysis

Results were expressed as mean and standard deviation (SD) or as median and interquartile range (IQR: P25-P75) for quantitative variables and as frequency tables for categorical variables. Mean values before and after treatment were compared by Student paired t-test or Wilcoxon signed rank test for skewed data. The McNemar and symmetry tests were used to compare paired proportions. Group comparisons were done by the unpaired Student t-test or Kruskal-Wallis test for quantitative variables and by the chi-squared or Fisher exact test for qualitative findings. The association between two continuous variables was measured by the correlation coefficient. Linear regression analysis was used to assess the effect of single or multiple patient baseline

characteristics on the evolution of pain scores and movement limitation. Results were expressed as regression coefficients with their standard error (SE). For ordinal outcomes (e.g. patient satisfaction), ordinal logistic regression was applied to data and the parameter effects were measured in terms of the odds ratio (OR) and its 95% confidence interval (95% CI). Ordinary logistic regression was used for binary outcomes (e.g. treatment continuation, resolution of tendinopathy). Statistical calculations were always based on the maximum number of observations available. Missing values were not replaced or imputed. Results were considered significant at the 5% level ($p < 0.05$). All analyses were performed using SAS statistical software version 9.4 (SAS Institute, NC, USA), and R version 3.6.1.

Results

Demographic data

The subjects were 55.9 ± 15.6 years old (range: 15 - 97 years) and 54.9% were female. The characteristics of tendinopathy are described in Table 1. Tendinopathy was most frequently located in shoulder (27.8%), knee (19.0%), elbow (16.9%), hip (15.7%), wrist (11.0%), Achilles tendon (10.4%), spur heel (5.7%) and thumb (4.6%). For the majority of patients (91.6%), a single location of tendinopathy was reported. Combined locations included wrist and thumb (0.9%), knee and hip (0.9%), and shoulder and elbow (0.9%). For almost half of the patients (46.5%), symptoms were present for more than a month. The most frequent causes of tendinopathy were repetitive movements in the daily life (52.5%), work (34.6%) and sport (24.0%). Combined causes were work and repetitive movement (8.5%), sport and work (1.8%),

and sport and repetitive movement (1.5%). Pain was present during movement in 53.1% of patients and all the time in 41.9%. The VAS pain score during the last 48 hours was 6.16 ± 1.53 mm and the VAS functional limitation (limitation in usual movements) score 5.96 ± 1.74 mm. A strong correlation was noted between pain intensity and functional limitation ($r = 0.70$, $p < 0.0001$).

Treatment history

Among the patients, 545 (81.3%) took at least one treatment at baseline. Specifically, 314 (46.9%) had oral NSAIDs (mainly ibuprofen or diclofenac or piroxicam), 270 (40.3%) painkillers (mainly acetaminophen or tramadol or traumeel), 207 (30.9%) topical treatment (topical NSAIDS mainly diclofenac or vanillyl butyl ether), and 44 (6.6%) at least another treatment (mainly rest, cold therapy, physical therapy or braces). For 95.7% of the patients, the recommended posology (2 caps of CBE in the morning and 2 caps in the evening) was prescribed for 4 weeks by the physician and followed the posology during the entire treatment period. After 1 month, 92% claimed to have respected the posology. Further, 414 (61.8%) took at least one concomitant treatment (paracetamol or NSAIDs) during the study period, specifically 250 (22.4%) had NSAIDs, 229 (34.2%) painkillers, 127 (19.0%) a topical treatment, and 62 (9.3%) another treatment.

Treatment effect

Pain

After one month oral treatment with CBE in addition to standard treatments, the pain score decreased from 6.16 ± 1.53 to 2.98 ± 1.64 ($p<0.0001$), yielding a drop of 51.6% (Figure 1A). The effect of treatment on pain was observed in both genders and whatever the cause of injury, the tendinopathy location, the symptoms duration and the intake of concomitant standard treatment. However, multiple regression analysis showed that it was higher in men than in women ($p=0.037$), lower in patients with a duration of symptoms of at least 2 weeks ($p=0.0021$) or at least one month ($p<0.0001$) compared to the other items. It was reduced in patients with pain at movement ($p=0.037$) or in patients with sustained pain ($p=0.013$) when compared to patients having pain at rest. Greater pain reduction was also noted for patients with higher pain scores during the past 24h at baseline ($p<0.0001$) and also to a lesser extent in patients taking at least one concomitant treatment at inclusion ($p=0.040$). Finally, the pain reduction due to treatment markedly decreased with to the number of NSAIDs medications taken by the patient at baseline ($p=0.0091$) (Table 2).

Functional limitation

Similarly, the motion limitation score fell after one-month treatment from 5.96 ± 1.73 to 2.88 ± 1.67 ($p <0.0001$) corresponding to a drop of 51.6% (Figure 1B). The improvement of functional limitation was observed in both genders, in all tendinopathy locations and whatever symptoms duration, concomitant treatment

intake, and cause of injury. By multiple regression analysis, it was found that the beneficial drop in functional limitation was more pronounced in men than in women (p=0.0093). However, it was lower in patients with a duration of symptoms of at least 2 weeks (p=0.013) or at least 1 months (p=0.0002) compared to the others. It was reduced in patients with sustained pain (p=0.031) when compared to patients with pain at rest. Similarly to pain scores, greater improvement in functional limitation was observed for patients with higher limitation scores during the last 24h at baseline (p<0.0001). No effect was observed for the other factors (Table 3).

Patient satisfaction

More than 76% of the patients were satisfied or very satisfied with the treatment, 18.5% were neutral and 5.4% dissatisfied. Satisfied patients were mostly male (OR 1.38; IC95% 1.01-1.87), with elbow (OR 1.97; IC95% 1.20-3.25) or Achilles' tendinopathy (OR 2.43; IC95% 1.31-4.50), with knee injury (OR 1.65; IC95% 1.01-2.70) and those with sport-related injury (OR 2.53; IC95% 1.43-4.47). The dissatisfied ones were preferably patients with symptoms duration > 2 weeks (OR 0.48; IC95% 0.28-0.82) or with symptoms duration > 1 month (OR 0.40; IC95% 0.25-0.68). Multivariate ordinal regression analysis of patient satisfaction confirmed these findings except for age (Table 4).

Among the patients, 431 (66.3%) wished to continue the treatment and 283 (44.0%) considered their tendinopathy as resolved. The desire to continue treatment increased with the patient's age (p=0.0024) and with symptoms duration (p=0.031). It was higher in patients with knee tendinopathy (p=0.038), in patient where the cause of injury was sport, work and/or repetitive movements, and in patients taking NSAIDs at

baseline (p =0.039). Patients who considered that the problem was not resolved were generally those with longer duration of tendinopathy (p=0.0062).

Concomitant treatments

The percentage of patients taking at least one concomitant treatment at the end of the treatment period had decreased from 81.3% to 61.8% (p<0.0001). This decrease was mainly seen for NSAIDs and topical treatments (Table 5).

Adverse events

Only 43 (6.5%) patients reported adverse effects. Among them, the most frequently reported was diarrhea (6 patients out of the 43). The others were mainly stomach pain (4/43), nausea (3/43), colored urine (2/43), flatulency (2/43), headache (1/43), bloating (1/43), constipation (1/43) or undescribed (14/43).

Discussion

The purpose of this observational, non-controlled study was to assess the benefit of support treatment with pharmaceutical grade CBE on tendinopathy. The patients, 344 women and 283 men, were on average 56 ± 16 years old. Most of them had shoulder, knee, elbow and hip tendinopathy and their symptoms were present for at least two weeks before food supplement prescription (Table 1). The pain was most often due to repetitive movement and the pain was most severe when the patient was in motion. On a visual assessment scale graduated from 0 to 10, the pain was on

average 6.2 ± 1.5 and the functional limitation due to pain 6.0 ± 1.7, values which can be considered as “moderate”. To the best of our knowledge, this study demonstrates for the first time that a food supplement combining Curcuma longa and Boswellia serrata extracts is effective to treat tendinopathy symptoms in addition to standard treatment.

After one month of treatment, the vast majority of the patients (92%) had followed their treatment and their pain decreased on average by 51 % on the visual scale (Figure 1A). The functional limitation score also dropped significantly by 51 % (Figure 1B). These effects can be explained by the anti-inflammatory activity of the active ingredients contained in CBE, as inflammation is related to pain and tendon extracellular matrix remodeling, mainly during the early phase. Indeed, inflammatory processes play essential roles in the pathogenesis of early tendinopathy. The tendon inflammation is accompanied by catabolic processes initiated by pro-inflammatory cytokines such as interleukin-1 β (IL-1 β) and tumor necrosis factor α (TNFα), which activate some signaling pathways in tenocytes including NF-kB signaling pathway. A recent in vitro study demonstrated that curcumin down-regulated gene products that mediate matrix degradation (matrix metalloproteinase-1, -9, and -13), prostanoids production (cyclooxygenase-2), apoptosis (Bax and activated caspase-3), and stimulated factor of cell survival (Bcl-2) in human tenocytes through the inhibition of NF-kβ signaling pathway (17,18). Curcumin, the main active ingredient of Curcuma Longa extract and boswellic acids contained in Boswellia serrata extract are all active on the synthesis and/or activity of these inflammatory mediators (25,26). Interestingly, patients taking NSAIDs at baseline responded better to CBE than those who did not. This supports the hypothesis that CBE is most effective in patients with inflammation at the beginning of the study. On the other hand, after one month of treatment with

CBE, the patients taking NSAIDs at baseline did not seem more satisfied than those who did not take them. We can explain this result by the hypothesis that the decrease in pain is not the only factor influencing the patient's satisfaction. Functional limitation is another possible factor. However, the improvement in functional limitation was not influenced by taking NSAIDs at baseline. This could explain, that despite an improvement of pain, patient taking NSAIDs at baseline were no more satisfied than those who did not.

Interestingly, pain relief was observed in all tendinopathy locations and irrespective of the cause of injury indicating that CBE may be helpful for a large panel of patients (Table 2). In addition, few patients had side effects (6.5%) and no interaction with other drugs was reported. This means that CBE may be used even in elderly patients with comorbidities, which is an advantage compared to NSAIDSs which are commonly prescribed for the treatment of tendinopathy (27). However, the long-term or recurrent use of NSAIDs is associated with numerous side effects, which can be quite adverse. Therefore, CBE could be an alternative to NSAIDs in the treatment of tendinopathy. Interestingly, CBE decreased NSAIDs consumption, suggesting that its effect is sufficiently clinically acceptable by the patient and limits the use of NSAIDs. Indeed, over three-quarters (76.1%) of the patients were satisfied or very satisfied with the treatment (Table 5). At the end of the study, 66.3% wished to continue this support treatment and, for 44% of them, the problem of tendinopathy was considered resolved.

The subjects satisfied with CBE were those suffering from elbow tendinopathy and those whose cause of tendinitis was linked to the practice of a sport (Table 4). On the other hand, the longer the duration of the symptoms, the lower was the patient’s satisfaction and pain relief, confirming an interest of this food supplement in the early phase of tendinopathy during the inflammatory phase. The role of inflammation and

its time course in tendinopathy has been addressed primarily in non-weight bearing shoulder tendons, suggesting that inflammatory mRNA biomarkers and cell infiltration can be demonstrated in the early phase of tendinopathy (28). However, in chronic prolonged tendinopathy it has been difficult to detect any signs of inflammation and anti-inflammatory medical treatment has not evidenced successful clinical outcomes. Thus, it is plausible that inflammation is primarily present in the early phase of tendinopathy where anti-inflammatory medication may play a role in the treatment strategy. Next to this short time effect we observed a smaller but still significant impact on pain and disability later on the pathology, suggesting a possible effect on tissue repairing in the later phase of the tendinopathy called late disrepair.

Many pharmacological treatments have been proposed for the management of tendinopathy, with no agreement regarding the overall best option available for all tendinopathy location and etiology. Thus, traditional treatment modalities aimed at controlling inflammation such as corticosteroid injections and nonsteroidal anti-inflammatory medications (NSAIDS) are not the best options as they are poorly efficient and associated with severe local or systemic adverse effects. In comparison with existing treatments, CBE offers the advantage to be non-invasive, safe and efficient on all tendinopathies. Of course, these encouraging results should be confirmed in larger randomized clinical trials and compared with those obtained with existing treatments. The concomitant use of CBE with other treatment modalities like shock wave therapy remain also questionable since it was demonstrated that curcumin has anti-coagulant properties. Globally, there is a lack of published well-performed randomized controlled trials comparing the various options available for the management of tendinopathy, studying large cohorts of patients for adequately long follow-up periods and with well-validated standardized scores and scales.

Conclusion

Pharmaceutical grade CBE at a prescribed dose of two tablets twice a day and in support to standard treatment was able to significantly reduce pain and functional limitation in early and chronic tendinopathy. After one-month treatment, there was a clinically relevant change for pain and functional limitation scores. Together with a significant reduction of concomitant NSAIDs intake and a good tolerability, these findings suggest that CBE is a potential support for treatment of tendinopathy even in elderly patients with comorbidities. Finally, this trial provides useful information for the design of a larger phase III clinical trial including the sample size estimate, the choice of the dose and the selection of primary outcomes.

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Figure legend

Figure 1: Effect of one-month CBE treatment on pain scores (A) and functional limitation scores (B) during the last 48h preceding assessment. A significant difference between baseline and one month treatment was observed with a p value <0.0001.

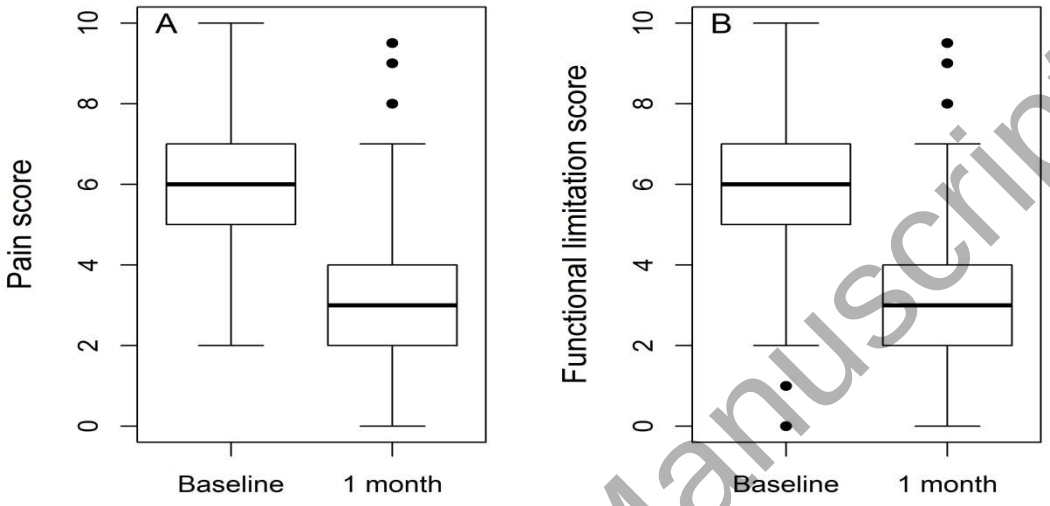

Table 1. Tendinopathy baseline characteristics (N = 670 patients)

Variable		N	Mean ± SD Number (%)	Range
Tendinitis location		670		
	Shoulder		186 (27.8)	
	Knee		127 (19)	
	Elbow		113 (16.9)	
	Hip		105 (15.7)	
	Wrist		74 (11)	
	Achilles' tendon		70 (10.4)	
	Spur heel		38 (5.7)	
	Thumb		31 (4.6)	
Pain history		666		
	< 1 week		72 (10.8)	
	1 to 2 weeks		115 (17.3)	
	> 2 weeks		169 (25.4)	
	> 1 month		310 (46.5)	
Cause of injury		662		2-10
	Repetitive movement		346 (52.3)	
	Work		229 (34.6)	
	Sport		159 (24)	
	Fluoroquinolones		4 (0.6)	
Type of pain		670		0-10
	During movement		356 (53.1)	
	All the time		281 (41.9)	
	At rest		33 (4.9)	
Pain during the last 48 h (0-10)		670	6.16 (1.53)	
Motion limitation during the last 48h (0-10)		670	5.96 (1.74)	

Table 2: Relationship between pain decrease after one-month treatment of CBE and variables recorded at baseline as derived from multiple linear regression applied to the study data (N=592). The multivariate coefficient of determination was R^2=0.38*.

Variable	Coeff (SE)	P-value
Age (years)	-0.006 (0.004)	0.18
Sex (male vs. female)	0.27 (0.13)	0.037
Tendinopathy location**		
Shoulder (yes vs. no)	-0.17 (0.18)	0.36
Achilles' tendon (yes vs. no)	-0.18 (0.24)	0.45
Knee (yes vs. no)	-0.07 (0.19)	0.70
Elbow (yes vs. no)	0.16 (0.20)	0.43
Wrist (yes vs. no)	-0.07 (0.22)	0.76
Hip (yes vs. no)	-0.35 (0.21)	0.10
Thumb (yes vs. no)	0.13 (0.31)	0.67
Spur heel (yes vs. no)	-0.17 (0.31)	0.60
Pain duration		
1 to 2 weeks (vs. < 1 week)	-0.42 (0.24)	0.076
> 2 weeks (vs. < 1 week)	-0.69 (0.22)	0.0021
> 1 month (vs. < 1 week)	-0.95 (0.21)	<0.0001
Cause of tendinopathy**		
Sport (yes vs. no)	0.42 (0.24)	0.079
Work (yes vs. no)	0.24 (0.20)	0.24
Repetitive movement (yes vs. no)	0.40 (0.21)	0.054
Fluoroquinolones (yes vs. no)	-0.36 (0.76)	0.63
Type of pain		
During movement (vs. at rest)	-0.59 (0.28)	0.037
All the time (vs. at rest)	-0.71 (0.28)	0.013
Pain score	0.71 (0.06)	<0.0001
Functional limitation score	-0.04 (0.05)	0.40
Concomitant treatment (yes vs. no)	0.47 (0.23)	0.040
NSAIDs intake	-0.37 (0.14)	0.0091
Painkillers	-0.11 (0.13)	0.39
Topical treatment	-0.27 (0.14)	0.056
Other treatments	0.42 (0.21)	0.046

*Results are expressed as regression coefficients with standard error; a positive coefficient corresponds to a bigger drop (improvement) in pain while a negative coefficient indicates a smaller decrease (deterioration) in pain

** Several locations and several causes can be reported by the same patient

Table 3: Relationship between functional limitation decrease after one-month treatment of CBE and variables recorded at baseline as derived from multiple linear regression applied to the study data (N=592). The multivariate coefficient of determination was R^2=0.40*

Variable	Coeff (SE)	P-value
Age (years)	-0.005 (0.005)	0.26
Sex (male vs. female)	0.34 (0.13)	0.0093
Tendinopathy location**		
Shoulder (yes vs. no)	0.08 (0.19)	0.65
Achilles' tendon (yes vs. no)	0.25 (0.25)	0.31
Knee (yes vs. no)	0.10 (0.19)	0.61
Elbow (yes vs. no)	0.29 (0.20)	0.15
Wrist (yes vs. no)	0.34 (0.22)	0.13
Hip (yes vs. no)	0.07 (0.21)	0.74
Thumb (yes vs. no)	-0.13 (0.32)	0.68
Spur heel (yes vs. no)	0.02 (0.32)	0.95
Symptoms duration		
1 to 2 weeks (vs. < 1 week)	-0.20 (0.24)	0.41
> 2 weeks (vs. < 1 week)	-0.58 (0.23)	0.013
> 1 month (vs. < 1 week)	-0.82 (0.22)	0.0002
Cause of tendinopathy**		
Sport (yes vs. no)	0.28 (0.25)	0.26
Work (yes vs. no)	0.07 (0.21)	0.72
Repetitive movement (yes vs. no)	0.16 (0.21)	0.46
Fluoroquinolones (yes vs. no)	-0.91 (0.78)	0.24
Type of pain		
During movement (vs. at rest)	-0.52 (0.29)	0.076
All the time (vs. at rest)	-0.63 (0.29)	0.031
Pain score	0.01 (0.06)	0.84
Functional limitation score	0.66 (0.05)	<0.0001
Concomitant treatment (yes vs. no)	0.24 (0.23)	0.30
NSAIDs intake	-0.14 (0.15)	0.33
Painkillers	0.05 (0.13)	0.69
Topical treatment	-0.10 (0.14)	0.50
Other treatments	0.44 (0.22)	0.039

*Results are expressed as regression coefficients with standard error; a positive coefficient corresponds to a bigger drop (improvement) in functional limitation while a negative coefficient indicated a smaller decrease (deterioration) in functional limitation

** Several locations and several causes can be reported by the same patient

Table 4: Relationship between improvement in patient satisfaction after one-month treatment of CBE and variables recorded at baseline as derived from multivariate ordinal logistic regression applied to the study data (N=592). The quality of the regression is given by the area under the ROC (AUC = 0.654)*

Variable	OR	IC95%	p-value
Age (years)	1.00	0.99-1.01	0.76
Sex (male)	1.06	0.75-1.50	0.73
Tendinopathy location**			
Shoulder (yes vs. no)	1.13	0.67-1.93	0.64
Achilles' tendon (yes vs. no)	2.04	1.02-4.08	0.043
Knee (yes vs. no)	1.66	0.96-2.85	0.068
Elbow (yes vs. no)	2.31	1.31-4.06	0.0038
Wrist (yes vs. no)	1.03	0.56-1.89	0.94
Hip (yes vs. no)	1.36	0.75-2.48	0.31
Thumb (yes vs. no)	1.38	0.60-3.20	0.45
Spur heel (yes vs. no)	1.15	0.48-2.73	0.76
Symptoms history			0.0010
< 1 week	1.00		
1 to 2 weeks	0.76	0.41-1.43	
> 2 weeks	0.40	0.22-0.74	
> 1 month	0.38	0.22-0.69	
Cause of tendinopathy*			
Sport (yes vs. no)	2.59	1.34-5.00	0.0046
Work (yes vs. no)	1.47	0.85-2.53	0.17
Repetitive movement (yes vs. no)	1.37	0.78-2.40	0.27
Fluoroquinolones (yes vs. no)	0.27	0.04-1.84	0.18
Type of pain			0.053
At rest	1.00		
During movement	0.74	0.35-1.56	
All the time	0.51	0.24-1.09	
Pain score	1.12	0.96-1.29	0.15
Functional limitation score	1.02	0.90-1.16	0.77
Concomitant treatment			0.55
Yes	1.00		
No	0.83	0.45-1.52	
NSAIDs intake	1.11	0.76-1.63	0.58
Painkillers	0.93	0.66-1.32	0.69
Topical treatments	0.83	0.57-1.21	0.33
Other treatments	1.18	0.67-2.07	0.57

*Results are expressed as odds ratios and 95% confidence intervals; an OR > 1 corresponds to a greater improvement in patient satisfaction while an OR< 1 indicates a deterioration in patient satisfaction

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Table 5: Evolution of the number of concomitant medications taken by the patients between baseline and one-month treatment with CBE (N = 670)

Medication		Mean number ± SD	P value
NSAIDs			
	Baseline	0.49 ± 0.55	
	After one month	0.23 ± 0.43	
	Change from baseline	0.27 ± 0.55	<0.0001
Painkiller			
	Baseline	0.43 ± 0.55	
	After one month	0.36 ± 0.52	
	Change from baseline	0.067 ± 0.49	0.0004
Topical treatment			
	Baseline	0.32 ± 0.49	
	After one month	0.19 ± 0.39	
	Change from baseline	0.13 ± 0.47	<0.0001
Other treatment			
	Baseline	0.072 ± 0.29	
	After one month	0.099 ± 0.32	
	Change from baseline	-0.027 ± 0.33	0.036