Original paper

Is the inflammation process absolutely absent in tendinopathy of the long head of the biceps tendon? Histopathologic study of the long head of the biceps tendon after arthroscopic treatment

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Tendinopathy of the long head of the biceps tendon is a difficult medical issue. Its pathogenesis and etiology is multifactorial and unclear. Tendinopathy is thought to be primarily degenerative in nature, as tendons are characterized by impaired regeneration and healing. Thirty–five patients with preoperatively diagnosed tendinopathy of long head of the biceps tendon were referred to the Orthopedics Department. All patients underwent an arthroscopic–assisted biceps tenodesis or tenotomy. The intra-articular portion of the long head of the biceps tendon was obtained from each of the patients who underwent arthroscopy. A macroscopic and microscopic evaluation of biceps tendon samples revealed degeneration among all specimens. This study demonstrates the prevalence of the degeneration process and the presence of marginal inflammation process in tendinopathy of the long head of biceps tendon. The role, that inflammation process plays in tendinopathy is important in the early phase and gradually becomes secondary to the developing degeneration. The inflammatory cells, occasionally seen in pathological tendons, could be an evidence of re–injury and recent healing response.

Key words: biceps tendinopathy, anterior shoulder pain, the long head of the biceps tendon, tendon inflammation, tendinopathy.

Introduction

Tendons are hierarchically organized structures optimized for transfer of loads in the locomotor system. Since they are subjected to repetitive loads of various magnitudes, their main components: tenocytes and extra-cellular matrix (ECM) need to adapt to changing mechanical conditions. Tenocytes play the main role in maintaining tendon matrix and synthesis of the collagen molecules; they maintain the homeostasis of ECM and continuously remodel it to optimize the fibrous structure with respect to loads applied to the tendon [1]. This mechano-biological response requires a constant interaction between ECM and tenocytes which is efficient at physiological ranges. However repetitive application of loads exceeding these values result in pathological alterations in tendon's structure and are one of main causes of their chronic failure [2].

Tendon after injury is repaired during three-step process, divided into inflammation, formative and remodeling phase [3]. The trigger factor – injury, promotes inflammatory process, which lasts about 7-8 days and is characterized by formation of hematoma in damaged area. In this time, the zone of injury, is rich in inflammatory cells: neutrophils, macrophages and platelets. After the inflammatory phase, the proliferative phase lasts up till about 21th day. In this period of time, there is a gradual reduction of inflammatory cells and progressive domination of tenocytes.

In contrast to acute injuries, which can result in healing, repetitive overloading leads to degeneration of tendinous tissue, which results in deterioration of biomechanical properties of the affected tendon. This process is called tendinopathy, and as demonstrated by several studies seems to be predominantly a result of mechanical damage associated with very limited inflammatory response. Tendinopathy is characterized by increased matrix remodeling, elevated activity and expression of metalloproteinases (MMPs), increased type III collagen contents, collagen degeneration and increased proteoglycans contents [2]. Chaotic production of ECM components by tenocytes and chaotic expansion of new capillary correspond to clinical symptoms such as chronic pain and spontaneous partial or full rupture. The etiology of tendinopathy is poorly understood and multifactorial. The main hypotheses on tendinopathy origin are: vascular, mechanical and nervous theory; it is however likely that it is the result of a combination of these three theories [3, 4, 5].

One of most common tendinopathies is the degeneration of the long head of the biceps tendon (LHBT). This may result from unique anatomy of LHBT, which is divided into two portions: extra-articular and intra-articular [2]. The intra-articular part of the LHBT is prone to degeneration due to its exposition to tear, compression and friction forces [2]. Interestingly, there is surprisingly little data regarding histological findings in this common condition. Moreover several reports indicated, that LHBT tendinopathy may be asymtomatic or associated with mild pain, and currently there is no clear link between microscopic changes within affected tendon and clinical symptoms.

The aim of this study is to conduct a histopathologic analysis of intra-articular parts of long head of the biceps tendons excised because of tendinopathy during arthroscopic biceps tenodesis or tenotomy. We wanted to verify the presence of inflammatory response in LHBT and determine if there is a relationship between microscopic findings and clinical data.

Material and methods

Thirty-five patients with clinically diagnosed LHBT tendinopathy and other shoulder pathologies (the most frequent were rotator cuff tears and subacromial impingement) were referred to Orthopedics Department and qualified for shoulder arthroscopy. The group consisted of 19 females and 16 males with a mean age of 53 years (28-75; SD 10.48). All patients met the following inclusion criteria: age 18-75 years, diagnosis of tendinopathy based on clinical examination and MRI (magnetic resonance imaging), no history of inflammatory rheumatic diseases. None of the patients had undergone surgical treatment or been treated with corticosteroid in the past 12 months. Since obtaining samples of healthy biceps tendons for use as controls is very difficult, we decided to obtain samples of healthy tendon tissue from subjects who undergo Anterior Cruciate Ligament (ACL) reconstruction using hamstring tendons, and did not manifest pathologies of semitendinosus or gracillis tendons.

The LHBT tendinopathy was diagnosed preoperatively and based on non-contrast MRI scans and physical examination performed by a specialist in orthopedic surgery, one day before shoulder arthroscopy. During this examination the type and duration of symptoms were recorded, and during a detailed physical examination tenderness over bicipital groove was specifically examined, as previously described [6].

In the examined group all patients underwent arthroscopic biceps tenodesis or tenotomy, according to techniques described previously [7]. Shoulder arthroscopy was performed in the beach chair position in general anesthesia. During the arthroscopy the LHBT was inspected for pathology and concomitant pathologies of the other structures, which were noted and recorded for further studies. Portions of intra-articular part of the LHBT were obtained from each of the patients who underwent shoulder arthroscopy. The intra-articular part of the tendon was removed by arthroscopic scissors about 1 cm from the origin point – at the supraglenoid tubercle, to the bicipital groove area; the residual part at the supraglenoid tubercle was removed by vaporization technique.

Control samples were fragments of semitendinosus (ST) tendon of 4 patients undergoing arthroscopic reconstruction of the ACL (4 males, age 38-49 years). We used fragments of the tendon discarded during preparation of the graft.

All harvested tissue samples were fragments were immediately placed in plastic containers with 10% buffered formalin and fixed overnight. Next samples were dehydrated in increasing concentrations of etha-

nol, cleared in xylene, embedded in paraffin, cut into sections of 4 μm thickness by microtome, mounted on glass slides. We used hematoxylin and eosin (HE) staining for routine histopathologic examination using an optical microscope (Olympus, model BX46, Tokyo, Japan) at magnification of 20×, 100×, 200× and 400×, non-randomly selected all area of slides. Additionally, specimens were stained with Alcian Blue, Mason and Mallory methods. These supplementary methods of staining helped to illustrate the accumulation of extra–cellular matrix.

In order to determine the extent of degeneration and inflammatory process in resected fragments we decided to examine the slides using the Bonar scale, which was also used by other papers regarding tendinopathies [8, 9]. This semiquantitative system evaluates four main variables: tenocyte morphology, changes in the ground substance and its accumulation, neovascularity and collagen bundles architecture. For each variable 0 to 3 points are attributed (0 – normal tissue, 3 – extreme pathology), which yields a total of 0 (normal tendon) to 12 points (most severe detectable abnormality). Additionally we quantified the number of inflammatory cells (lymphocytes, macrophages and neutrophils) on the entire area of all slides.

All procedures described in the study were approved by Local Ethic Committee – KB 598/2016. All patients were volunteers and gave informed consent. Surgical procedures were performed by ASz, ŁP and JZ; microscopic examination by JSz, DG and JZ.

Results

The duration of symptoms was less than 1 year among 11 subjects, more than one year and less than two years among 10 subjects and longer than 2 years in a group of 14 subjects. All patients admitted, that they occasionally took NSAID (non-steroidal anti-inflammatory drugs) because of their shoulder pain. Preoperative physical examination showed that, palpation in the bicipital groove was painful in 33 of 35 subjects. The two asymptomatic cases were a 52 years old male with complete medial dislocation of LHBT (Bonar score 8), and a 65 years old male with complete LHBT rupture (Bonar score 11).

Arthroscopic investigation of the affected shoulders revealed that only three patients had isolated LHBT lesion (Bonar score 5, 5, 8 points respectively), in other cases we found concomitant pathologies, such as rotator cuff tears (RCTs) in 24 patients, subacromial impingements in 18 patients and labral defects in 2 patients. During shoulder arthroscopy 7 patients underwent the tenotomy procedure and 27 patients underwent the tenodesis procedure, there was one stub resection due to previous the LHBT complete rupture. There was no different anatomic variants of LHBT origin's found in the study.

Macroscopic evaluation of the LHBT samples showed signs of degeneration among all specimens: visible tears, fraying, widening and flattening, gray – yellowish discoloration of the tendons (Fig. 1). Mean length of samples was 12.3 mm (range 5-20 mm) of the length and , their mean diameter was 6,8 mm (range 3-15 mm).

Microscopic evaluation of H&E staining slides showed advanced degeneration in all specimens (Figs. 2 and 3). After examination according to Bonar scale, grades 2 and 3 in tenocyte morphology were identified in 24 of 35 samples (Table I). In these patients the morphology of tenocytes was altered; there was an increased number of enlarged, rounded cells, with enlarged nuclei and decreased amount of cytoplasm (Fig. 3C, 3D). In these samples tenocytes were randomly scattered in the tissue, their organized distribution typically seen in healthy tendons was lost. Grades 2 and 3 in collagen bundle characteristics were identified in 30 of 35 samples (Fig 3A, 3B). Overwhelming disorganization of the longitudinal alignment of collagen fibers was found. We noted separation of collagen bundles, loss of characteristic "crimping pattern", and disorientation of the fibers. Degeneration of the ground substance (Grade 2 and Grade 3) was identified in 34 of 35 specimens (Fig. 3A-D). Ground substance was accumulated mainly between collagen bundles, separating them.

Fig. 1. Macroscopic evaluation of the tendon samples and measurement. Macroscopic features of degeneration: visible damage to the structure, flattening, color change

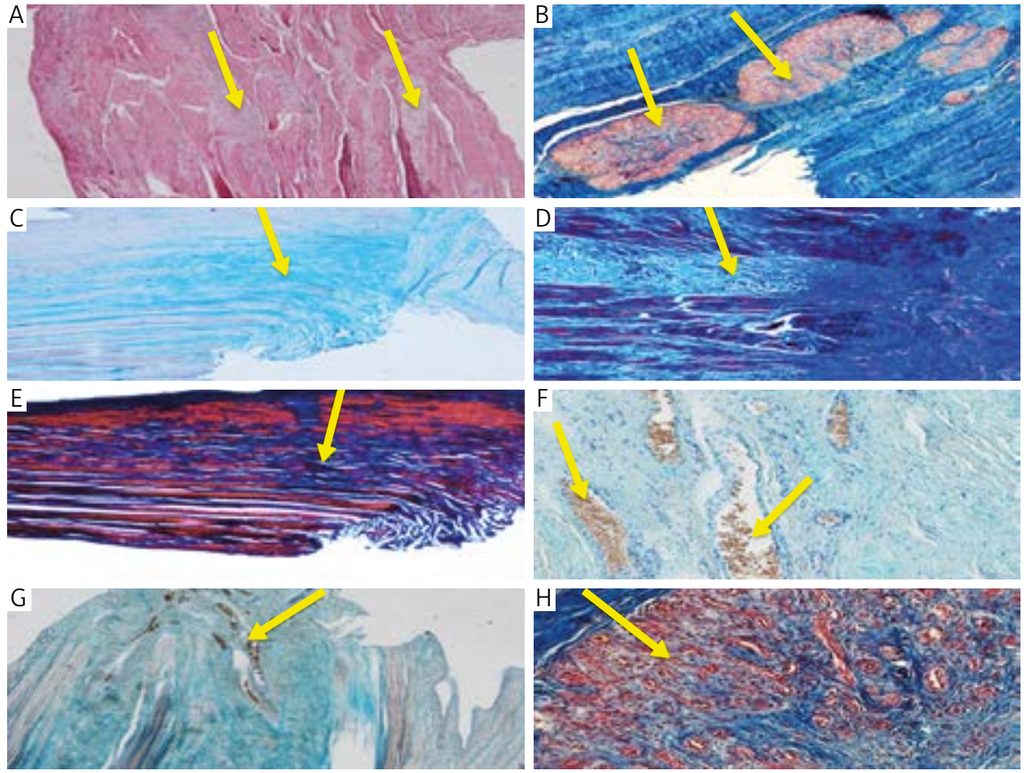

Fig. 2. Microscopic evaluation of specimens: A) Disorganized collagen, separation and disorientation of fibers. Expansion of extracellular matrix – yellow arrows. (HE, magnification 20×). B) Abundant vascular proliferation with clusters of capillaries – yellow arrows. (Mason, magnification 100×). C) Alcian Blue, magnification 20×; D) Mason, magnification 20×; E) Mason, magnification 20×. Myxoid ground substance between disorganized collagen bundles– yellow arrows. F) Stain: Alcian Blue, magnification 100×; G) Alcian Blue, magnification 20×; H) Mason; magnification 100×. Proliferation of vessels – yellow arrows

Neovascularization was present in 28 of 35 samples with Grade 2 and 3 found in 23 specimens (Fig. 2B, F, G, H). Groups of capillary vessels were distributed randomly and chaotically. One sample demonstrated abundant granulation tissue with blood vessels consolidated in clusters.

In the examined cohort, mean Bonar score was 8.2 (range 4-11 and SD – 2). In three samples we noted presence of modest infiltration of inflammatory cells around blood vessels cells: in two patients the infiltration consisted of lymphocytes, in one patient of neutrophils. Despite the invasion of inflammatory cells, microscopic analyze of LHBT samples revealed advanced degenerative response of tissue – Bonar 7, 10, 11 points respectively.

This group included three patients: a 52 years old male with SST and SSC tendon lesions and LHBT thickening (symptoms since 1 year, Bonar score 7), a 60 years old female with SST tear and LHBT degeneration (symptoms since 1 year, Bonar score 10), and a 49 years old male with subluxation of thickened LHBT (symptoms since 6 months, Bonar score 11). Based on data from medical history, clinical and microscopic examination we were unable to explain the cause of inflammatory infiltration in these patients (Table II).

All control samples included in this study had a macroscopic appearance of healthy tendons with brilliant white color. Microscopically all samples were characterized by low density of elongated, spindle–like tenocytes; characteristic "wavy configuration" of collagen fibers with their axial orientation and non-separation of bundles; few capillary vessels were found, with no visible vascular expansion. The Bonar score for these samples was 0 and inflammatory cells were absent (Fig. 4).

Discussion

Although damage to tendinous tissue related to mechanical overload is typically referred to as tendi-

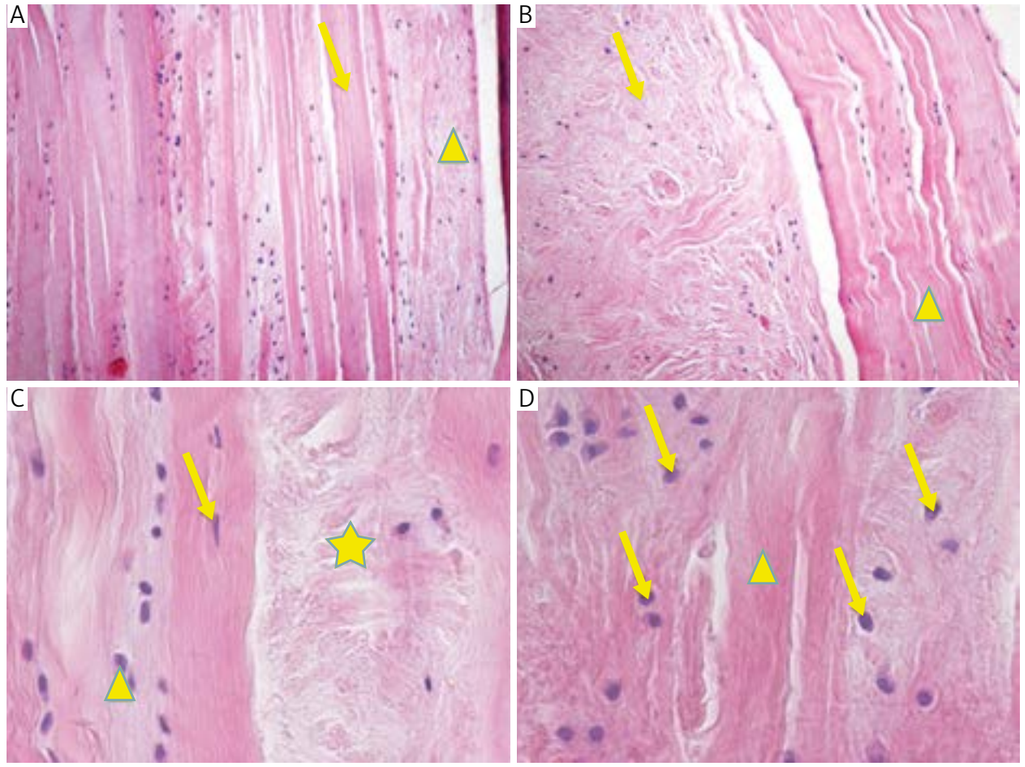

Fig. 3. Microscopic evaluation of specimens. A) Separation of collagen fibers by accumulated ground substance – arrowhead. Loss of characteristic "crimping pattern" of collagen fibers – arrow (HE; magnification 100×). B) Pathological accumulation of extra–cellular matrix – arrow. Loss of architecture of collagen fibers – arrowhead (HE; magnification 100×). C) Accumulation of ground substance – asterisk; spindle-shape normal tenocyte – arrow and rounded-shape pathological tenocyte – arrowhead (HE; magnification 400×). D) Pathologically transformed tenocytes – arrows; accumulation of ground substance – arrowhead (HE; magnification 400×)

nosis, this term may be misleading, since the inflammatory process implied by the name is usually mildly marked, and the degenerative process seems to play the main role [4, 10, 11, 12, 13]. Most authors described pathological tendon tissue as amorphous, grey or yellow, locally thickened, with deteriorated structure, and reported several microscopic features, such as disorganized ECM, presence of neovascularization and rounded tenocytes (Fig. 5) [2, 5, 14]. Interestingly, there is relatively little data regarding histology of LHBT degeneration and the relationship between microscopic findings or clinical symptoms. In this study we examined a series of LHBT tendons resected during shoulder arthroscopies to verify presence of microscopic signs of inflammation and degeneration; additionally link these findings with clinical symptoms.

Similarly as previous reports regarding tendinopathies in humans, our study is limited in several ways. The most important limitation comes from the fact that our group is not homogenous, since we included

Table I. Distribution of scores according to Bonar scale

Varaible/Grade according to Bonar score	0	1 point	2 points	3 points
Tenocytes		11 samples	21 samples	3 samples
Ground substance		1 sample	16 samples	18 samples
Collagen disorganization		5 samples	17 samples	13 samples
Neovascularisation	7 samples	5 samples	10 samples	13 samples

Table II. Comparison of subjects with inflammation and degeneration

Pathology recognized in microscopic examination	Number of subjects	Mean Bonar score in a group	% of positive clinical test	Additional pathologies found during arthroscopic investigation
Inflammation with degeneration	3	9.3	100	2 RCTs, 1 SI
Alone degeneration	32	8.1	94	22 RCTs, 17 SI, 2 LD 3 patients with isolated LHBT pathology

LD – labral defects; SI – subacromial impingement

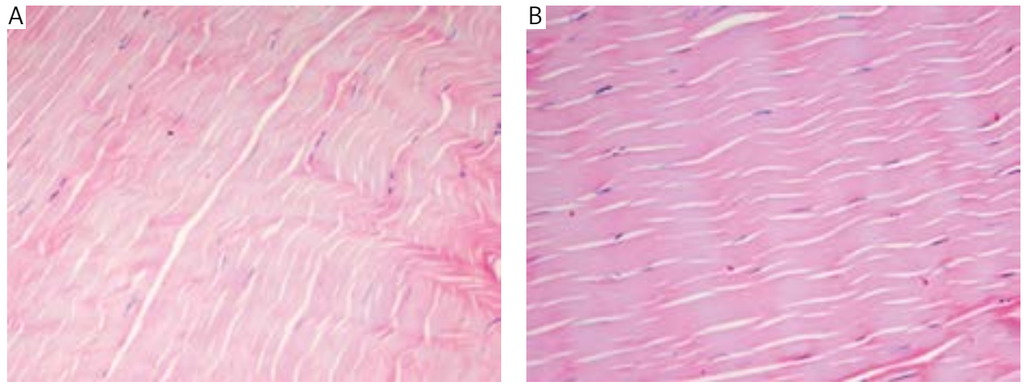

Fig. 4. A, B) Negatvie controls obtained from semitendinosus tendons. Organized structure and characteristic configuration of collagen fibers; elongated-shape tenocytes.(Stain: hematoxylin and eosin; magnification 100×)

patients with different shoulder pathologies; moreover in some patients pathological changes may also be related to old age [15]. This could have biased our results, since it is possible that patients with isolated LHBT pathology the extent of degeneration could be different than in this study, however since isolated cases of LHBT pathology are rare, most studies regarding this tendon included a group of patients similar to ours [2, 9]. Due of ethical reasons we included hamstring tendons from healthy individuals as controls. These samples had microscopic characteristics of healthy tendons, however we cannot exclude, that in patients with asymptomatic and macroscopically intact LHB tendons some pathologies could be detected at microscopic examination. Previous studies were also limited this way; some authors included samples from cadavers, however in such cases microscopic findings may be biased by post mortem tissue degeneration; it was also impossible to verify clinical symptoms. Lastly, our study was based on semiquantitative scoring system which can be affected by subjective differences between observers. In order to avoid this samples were examined by three authors, similarly as in other studies.

Currently two main classifications are being used to evaluate histopathological alterations in tendinopathies: Bonar and Movin scores [16]. The most important difference between these systems is the evaluation of hyalinization, in the Movin scale, which was primarily designed for Achilles tendon pathology, where hyalinization is often seen. This criterion is not included in Bonar scale used in this study, however this choice is unlikely to bias our results, since hyalinization is rare phenomenon in LHBT tendinopathy. Moreover, Bonar score was also validated by authors studying tendons of the upper and lower extremity [10].The utility of Bonar score was also demonstrated in SST and patellar tendon pathology [8, 17].

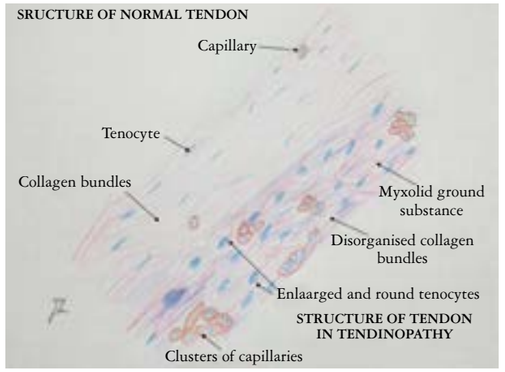

Fig. 5. Draft showing differences between normal tendon and tendon involved in degeneration process

Our study demonstrated presence of a degenerative process in the affected LHBT tendons, which involved both the tenocytes and extra-cellular matrix. Khan *et al*. have summarized histopathological findings in tendinopathies, affecting the Achilles tendon, patellar tendon, extensor carpi radialis tendon, rotator cuff tendons [13]. Their analysis of multiple studies showed prevailing degenerative disorders in the development of tendinopathy process. More specific results regarding LHBT were presented by Streit *et al*., who investigated samples of extra–articular portions of the LHBT, obtained from patients who underwent open subpectoral tenodesis [10]. Their results – prevailing degeneration process, assessed by mean of modified Bonar score, were similar to ours.

Joseph *et al*. have described a similar microscopic and macroscopic findings during the evaluation of the intra–articular portion of the LHBT, which displayed numerous features of tendinopathy such as collagen disorganization with loss of crimps,myxoid ground substance accumulation and expansion of new capillary vessels [2]. Since these authors focused on expression of certain proteins such as collagen III type, MMP (1, 2, 3, 13), IGF-1, they did not classify morphological alterations using semiquantitative scoring systems.

Historically, it was believed that tendinopathy is driven by an inflammatory process, which results in lesions observed microscopically [14]. Evidence from more recent studies suggests, that the predominant role can be attributed to the degenerative process and inflammation is of a lesser importance. It is thought, that the inflammatory component is present in the beginning of tendinopathy, as demonstrated in studies using animal models; it must be however noted that this cannot be directly extrapolated to humans, since human studies are limited in the initial phase [5, 14]. Data from studies regarding traumatic lesions indicates, that the acute phase after injury, when the tendon's healing process is starting, can last for about 21 days. This phase involves inflammatory response, infiltration and gradually transforms into the remodeling phase (from 3-6 weeks till 1 year), which is characterized by decreased number of cells and organizing of the collagen fibers structure [3]. The transition from acute injury to chronic pathology was studied to a much smaller extent, and most studies published so far focus on the Achilles tendon.

Schubert *et al*. revealed demonstrated presence of macrophages and lymphocytes (using immunohistochemical techniques), in a chronic Achilles tendon pathology (duration of symptoms was 6-120 months) and granulocytes in a short time after acute rupture of the Achilles tendons [18]. Other authors demonstrated indirect signs of inflammatory response found in chronic tendons disorders – mediators of inflammation: IL-1, IL-6, TGF-β, substance P [19]. A smaller body of literature exists on chronic LHBT pathologies. In a study of LHBT samples obtained during arthroscopy Streit *et al*. noted chronic inflammation among 2 of 26 specimens, however no signs of acute inflammation were noted in any patients from their study [10]. This is similar to our study, where some patients exhibited signs of inflammatory infiltration, however data from a study by Murthi *et al.* revealed chronic inflammation in 63% of shoulder with RCTs and LHBT tendinopathy [20]. They noted significant correlation of pathological changes with pain. Authors examined 200 patients and found 1% of acute inflammation, 63 % of chronic inflammation among specimens. In a different study, Longo *et al.* examined LHBT obtained from 51 patients, that underwent shoulder arthroscopy with diagnosis of LHBT tendinopathy [21]. Advanced degeneration was noted among biceps tissue portions, however there was a striking absence of inflammatory cells.

Based on the duration of symptoms in our cohort, which exceeded several months and the fact that most of our patients reported no singular traumatic event, but rather related their pain to activities related to work, we hypothesize, that the inflammation was not related to acute injury, however data obtained during clinical examination and microscopic analysis was insufficient to explain the cause of such reaction in these patients. Additionally, data from the literature regarding prevalence of inflammatory reaction in LHBT tendinopathy is conflicting and most papers did not provide information regarding duration of symptoms in such cases.

So far in most cases of LHBT tendinopathies anti-inflammatory methods of treatment have been used as a first choice. Given the fact that most studies did not demonstrate presence of a inflammatory process this is becoming controversial, particularly corticosteroids injections, especially since a high percentage of unsuccessful cases have been reported [1, 14]. Similarly, this can explain why the use of non-steroid anti-inflammatory drugs (NSAID) may be ineffective in LHBT pathologies. This is illustrated by a review of literature focused on 32 studies evaluating effectiveness of NSAID in tendinopathy, whereas 9 of 32 were prospective and placebo controlled and only 5 of them revealed reduction of painful conditions [22]. Different study investigated effectiveness of corticosteroids injections – only short–term clinical improvement was reported [19]. Authors point at the side-effects of corticosteroids injections: skin atrophy, decreased tendon strength and integrity, infections, possibility of spontaneous tendon rupture.

Since histological studies indicate that the degenerative process, rather than inflammation is the main failure mechanism in LHBT tendinopathy, the question arises, what leads to painful condition of the tendon? One of possible explanations arises from the fact, that expansion of new capillaries, which is a characteristic feature of tendinopathy [14, 23].The ingrowth of the new vessels, known as neovascularization, is not present in healthy tendons. Numerous authors noticed, that in chronic tendinopathy, the abundant angio–fibroblastic response often connects with painful conditions [4, 23, 24]. During capillary vessels expansion, nerves endings penetrate the tendon's tissue – with a predominance of the sensory and autonomic nerves fibers [14, 25, 26]. Our study demonstrated advanced neovascularization process among 80% of specimens and positive clinical test among 90% of subjects, despite absence of any inflammatory process. Similarly Streit *et al.* did not find the correlation between pain and inflammation in the LHBT due to limited inflammatory response [10].

Summary

Biceps tendinopathy is not a very common issue in literature, although it is a widespread phenomenon and medical problem. The development of shoulder arthroscopy put the phenomenon of the chronic tendinopathy in a new light and allowed the non–invasive treatment of the LHBT disease. Morphological and histochemical analysis of the LHBT portions obtained from patients, revealed advanced tendinopathy in each case. We showed, that inflammation is not absent, but its role is marginal and is not associated with painful conditions. Important fact is, that inflammation and degeneration processes exist parallel and create the tendon pathology. Our understanding of the LHBT degenerative process is still improving because with each advance in the diagnostic and treatment field we are one step closer to resolve the problem of tendinopathy.

The authors declare no conflict of interest.

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