Clinical significance of spondyloarthritis-attended enthesites: from pathophysiology to treatment (review)


Abstract. The article presents the latest views on entheses’ anatomy and pathogenesis, clinical features, diagnostic and therapeutic options. The enthesis lesions are considered an outstanding pathologic and clinical manifestation of spondyloarthritis group; this symptom is included into the classification criteria by the Assessment of SpondyloArthritis International Society for the peripheral and axial forms. The typical spondyloarthritis-attended entheses’ localizations are: the site of Achilles tendon and plantar aponeurosis’ attachment to the calcaneus, the lateral condyle of the humerus, the medial condyle of the femur, the upper edge of the patella, the upper edge of the iliac bones, trochanters of the femoral bones, sinus processes of the vertebrae. The structures focused in the entheses’ sites have anatomical, functional and physiological interactions and constitute a single synovial-enthesal complex. Unlike the rheumatoid arthritis with a key pathological process occurring in the synovial lining, the spondyloarthritis is mainly provoking the morphological modifications, namely entheses, while the developing arthritis (synovitis) appears secondary to entheses. The enthesis is detected in 30–50 % of spondyloarthritis patients and associated with a higher activity, higher pain indices and a compromised life quality. The presence of entheses in the psoriatic arthritis patients is associated with axial and peripheral joint lesions, a high chance of ankylosation, a high disease activity, pronounced pains, a compromised life quality and functional state, sleeping disorders. Furthermore, the enthesis is considered a precursor of the negative disease outcome, and may forecast a lower probability of remission and a low activity. The enthesal inflammation occurs as a result of mechanical and/or infection-originating stress, resulting in the prostaglandin E2 and interleukin-23 activation with a further vasodilatation, and T-cell and Group 3 innate lymphoid cell (ILC3) activation. The innate immunity-generated inflammation is characterized by a release of tumor necrosis factor and interleukin-17, resulting in the immune cell influx, namely the polymorphonuclear neutrophils. Under the influence of interleukin-17 and interleukin-22, the mesenchymal proliferation is characterized by an activation and proliferation of resident mesenchymal stem cells in the periosteum. The enthesitis treatment strategies remain undefined; however, the ones most commonly used are the nonsteroidal anti-inflammatory drugs (NSAIDs), localized glucocorticoid injections, Apremilast, as well as targeted medications, namely the tumor necrosis factor, interleukin-17 and interleukin-23 inhibitors.

Keywords: enthesitis; spondyloarthritis; psoriatic arthritis; synovial-enthesial complex; prostaglandin E2; inflammation; pathogenesis; treatment

The enthesis is an area of tendon’s, ligament’s or articular capsule’s attachment to the bone. Although the enthesopathies are traditionally viewed as focal, insertion disorders, the magnetic resonance imaging (MRI) data and ultrasound examination suggest the presence of massive diffuse changes engaging the adjoining bone and soft tissue [1]. The enthesis lesions are referred to as a remarkable pathological and clinical sign of spondyloarthritides; this symptom is included on the list of the Assessment in SpondyloArthritis International Society (ASAS) classification criteria for peripheral and for axial forms [2]. With psoriatic arthritis (PsA), the presence of enthesitis, even with no arthritis or spondylitis observed, suggests the CASPAR criteria (2006) used for diagnosis of psoriasis patients at the early stage of this condition [3]. The typical spondyloarthritis-attended enthesitis localizations are the following: the site of Achilles tendon and plantar aponeurosis attachment to the calcaneus, lateral process of humeral bone, medial process of hip bone, upper edge of the iliac bone, hip bone trochanter, vertebral spinous processes. In order to assess the ankylosis-spondylitis-related enthesis condition from the clinical perspective, one should use MASES (Maastricht Ankylos-
The entheses are key structures enabling the transfer of mechanical forces from muscles to bones and thus serving as mobility tools. While the joints are in charge of the overall bone system’s mobility, the entheses are transforming the mechanical forces and providing stability. The entheses are usually localized beyond the joints in the periarticular zone or further away from any synovial joint. Overall, the human body has over 100 entheses connecting the “soft” connective tissue components (tendons, ligaments, synovial membranes etc.) to the “hard” skeletal tissue (bone) [6]. These structures have anatomical, functional and physiological bonds, may be viewed as one synovial-entheseal complex, a separate organ with a high metabolic activity. The inflammatory process — enthesitis — develops along with immune disorders. For instance, the enthesial sites of healthy mice demonstrate a double negative T-cell expression of interleukin-23 (IL-23R) (CD3⁺-CD4⁻-CD8⁻-IL23R⁺-cells) [7]. It is suggested that by contrast to the rheumatoid arthritis (RA), the ankylosing spondylitis and spondyloarthritis are associated with enthesitis-based morphological changes, while the developing arthritis (synovitis) is a secondary feature. The functional model of entheses is presented by Fig. 1. The knowledge of entheses’ anatomical characteristics is important for understanding the inflammatory process, which is associated with enthesitis, and is dramatically different from synovitis (synovial lining inflammation).

The enthesitis is observed in 30–50 % of spondyloarthritis patients [8]. It is associated with a more significant
activity, higher pain indices and a compromised life quality [9]. The enthesitis is a common PsA symptom; the PsA patients are four times as likely to be presenting entheses’ lesions at the ultrasound examination as the ankylosing spondylitis patients [10]. The recent studies [11] demonstrate that the present clinical enthesitis was associated with a higher disease activity and more compromised life quality than no enthesitis; the enthesitis patients were receiving a combined therapy more frequently, i.e. they had graver or aggravated forms of disease. Furthermore, the enthesitis is more frequently associated with a female (50 %) than a male gender (32 %) [12]. The enthesitis observed in the PsA patients may attend the axial and peripheral joint injuries; there is a high likelihood of ankylozation, the overall higher disease activity, pain intensity, more compromised life quality and functional state, sleep disorders and more intense fatigue reported by the patients [13, 14]. Furthermore, the PsA-attended enthesitis is considered a harbinger of negative disease outcomes and may forecast a smaller likelihood of remission and low disease activity [9, 15]. At the moment, the entheses are referred to as a key inflammation target with such musculoskeletal diseases as PsA and spondyloarthritis [6].

The enthesitis may result from a series of repeated mechanical overload strains, such as, for instance, those afflicting the professional athletes: “tennis elbow” or “golfer’s elbow” being typical examples of an isolated enthesitis caused by a mechanical overload. In those cases, the enthesitis has a localized character (damaging only one enthesis) and often resolves spontaneously. However, enthesitis is also a pathognomonic PsA and spondyloarthritis sign; it occurs quite often, has a multiple relapsing character and a tendency to chronization [16]. The reasons for spondyloarthritis patients’ susceptibility to enthesitis are not entirely clear. At the same time, there is no conclusive evidence that PsA and spondyloarthritish-attended enthesitis engages dramatically different mechanisms and processes if compared to the mechanical overload (for instance, the “tennis elbow”). However, one may assume that the threshold for enthesal inflammation’s initiation is much lower than the one of the PsA and spondyloarthritish patients, i.e. promoting enthesitis with the minimum mechanical effect or no effect at all. It is well-known that similar processes occur with a present psoriatic skin disease, i.e. significant skin reaction occurring at a minimum irritation/injury. For instance, Koebner phenomenon describes an emphasized and long-standing inflammatory skin reaction to the mechanical irritation of psoriatic patients.

On extrapolating this phenomenon to the musculoskeletal system, we may hypothesize that enthesitis of PsA and spondyloarthritish is a pathologically enhanced body response to any stress. However, the reason of a low enthesal inflammation threshold in PsA and spondyloarthritish patients is only assumed but not confirmed. The entheses contain a specific immune microenvironment activated by a combination of factors, such as mechanical stress,
genetic susceptibility and microorganism-generated immune activation. The potential explanation of enthesal inflammation includes such genetic factors, as Class I histocompatibility genes and IL-23R polymorphisms (encoding IL-23R (IL-23R) receptors), resulting in a long-term enhanced immune activation [17], epithelial barrier permeability due to the subclinical psoriasis (PsA) and colitis (spondyloarthritis), skin and intestinal microbiome disorders, microorganism effect and developing immune response [18].

The clinical observations ascertain that the mechanical effect/load induces enthesitis, which is why leg enthesitis occurs more frequently than arm enthesitis; the legs are subject to a frequent overload and injury. This concept is confirmed by the experimental studies where the mice relieved of the mechanical overload started to demonstrate a reduced enthesis of Achilles tendon [19]. However, there is no accurate description of molecular process generating mechanical injury and enthesal inflammation.

Prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) has an important role of an early enthesitis mediator (Fig. 1). This role is confirmed by a fast and powerful response of the axial and peripheral enthesis to the nonsteroidal anti-inflammatory drug (NSAID) treatment. The localized PGE<sub>2</sub> production may ensure a fast response to the mechanical overloading or other enthesis triggers. The resident mesenchymal cells are expressing the inducible Prostaglandin G/H synthase 2 (also known as Cyclooxygenase 2), explaining the localized PGE<sub>2</sub> production; the latter being principal Cyclooxygenase 2 (COX-2) product [20]. The PGE<sub>2</sub> has a vasodilatating effect, i.e. may result in a widening of trans-cortical vessels and promote the neutrophil transfer from the bone marrow to entheseal site. This fact explains the developing inflammatory response in the adjoining bone marrow (osteitis), and may be confirmed by MRI results in the PsA and spondyloarthritides patients. Furthermore, the PGE<sub>2</sub> promotes the IL-17 production by T-cells, which is why at the initial stage the inflammatory response is attributed to the IL-23/IL-17 pathway activation.

The mechanistic trials involving mice suggest that it is the IL-23, produced by macrophages and dendritic cells, which plays a vital role for enthesitis. This is why, excessive IL-23 expression in vivo may provoke enthesitis, even with no mechanic overload [21]. It is worthy of note that entheses have T-cells expressing IL-23R. The T-cell phenotyping prompted that they are γδ T-cells. These cells are the key cellular IL-17 and tumor necrosis factor (TNF) sources [22]. It is interesting to discuss the so-called Group 3 innate lymphoid cells (ILC3), which are expressing IL-23R, producing IL-17; the ILC3 are detected in normal entheses [23]. However, their role in developing the spondyloarthritides-attending enthesitis is not ascertainment.

The IL-17 production per se is a cornerstone of inflammatory response in the entheses under spondyloarthritis. The IL-17 promotes neutrophil migration and activation, i.e. the process, observed with psoriatic skin diseases, which unites the IL-23/IL-17 axis activation with an effector phase of inflammation [24]. The IL-17 is an enthesal inflammation enhancer and various cytokine and mediator inducers in charge of neutrophil migration and activation. The latter involve anti-inflammatory cytokines, such as granulocyte-macrophage colony-stimulating factor, IL-6 and IL-8; the latter being a key neutrophil chemoattractant. This is why neutrophils are considered the key effector cells involved in the enthesal inflammation. The enthesal neutrophils exacerbate the inflammatory response, releasing protease and active oxygen forms, intensifying the pain reaction and inflammatory process per se. Furthermore, the macrophages are able to infiltrate the enthesal tissue, expanding the inflammation site [25].

The enthesal inflammation is characterized by a pronounced tissue response. The local bone formation plays a key role in this event. As a result of inflammation, the entheses are facing false erosions; however, most commonly the new bone formation is followed by a peristomal response and enthesophyte formation [26, 27]. For instance, once the anterior and posterior vertebral areas are injured, syndesmophytes are formed, bringing along the spine ankylosis and a typical X-ray–registered image of “bamboo spine”. Upon the plantar fascia injury, an excessive bone formation results in a “metatarsal spur”. With PsA, the enthesophytes are formed in the peripheral joints and hand joints; this being a specific feature of psoriatic lesion, emphasizing enthesitis’ roles an early PsA feature [27].

The new bone formation is a tissue response starting after the enthesal inflammation peak being reached. This process is virtually initiated by the mesenchymal stem cells (MSCs) capable of proliferation and differentiation into chondroblasts and osteoblasts with a cartilage and bone being formed accordingly. Some researchers are comparing the new bone formation following enthesal inflammation with a post-fracture synostosis: the process being characterized by a fast and powerful response of mesenchymal tissue after an acute inflammation phase [28]. The cytokines and signal molecules binding the inflammatory and proliferative phase of enthesitis have not yet been fully detected; however, one suggests IL-17, IL-22, PGE<sub>2</sub> contribution as these agents demonstrated their capacity of mesenchymal cell activation in a series of experiments [29, 30]. For instance, the PGE<sub>2</sub> turned out to be an osteoblast differentiation activator, and in this capacity it may tie the enthesal inflammation with a new bone formation [31]. It is interesting to note that the TNF may impede the bone formation via its antianabolic effect, namely the sclerostin and Dickkopf-dependent protein 1 (DKK1) induction, as these two agents are well-known for their bone formation blocking capacities [32].

The initial process of new bone formation is not fully clear; however, the process of osteoblast and chondroblast differentiation is rather well researched. The leading role of Hedgehog-signaling pathway was first described in Droso phila fruit flies. The name “Hedgehog” refers to a characteristic mutation, constantly activating the pathway, the fruit fly larvae started resembling hedgehogs. The pathological activation of Hedgehog-signaling pathway accen-
tuates the cell proliferation and promotes apoptosis resistance. The Hedgehog-signaling pathway proteins activate a certain cell population, i.e., the effectors of Hedgehog (Hh) signaling (GLI1) regulating the transcription factor. These are the cells with a significant potential of mineralized fiber formation, and their activity is regulated by the muscle strain [33]. It is hypothesized that this pathway activation plays a vital role in the osteoarthritis-generated osteophyte formation [34]. In the enthesis, there is a peptide associated with a parathyroid hormone-related protein (PTHrP), which supports the bone cell activity and may participate in the induced bone formation [35]. The process of osteoblast differentiation and new bone formation is maintained by the bone morphogenetic proteins and Wnt signaling pathway proteins.

The PsA-associated pathogenetic value of enthesitis remains fairly topical. The PsA pathogenesis is not yet entirely clear. One model suggests that the T-lymphocyte response to a prevalent skin and synovial membrane antigen triggers an inflammatory process; this concept being confirmed by enthesitis interaction with HLA-DR17 [36]. Another model theorizes that enthesis is a factor initiating a congenital immune response [37]. The synovial-entheseal complex is inclined to face the microinjuries under the mechanical strain, provoking a congenital immune response to the inflammation being spread to the adjacent synovial lining [37]. In the entheses, we observe certain modifications, namely hypertrophic fibrocartilage cluster formation and matrix cracking. It is confirmed that under the natural conditions excessive IL-23 expression is fully responsible for enthesitis, psoriasis and sacroiliitis in the untreated B10.RIII mice. The CD3+CD4-CD8-IL-23R-native entheseal cells are reacting to the IL-23 and this reaction results in the IL-22 inducing the osteoproliferation via STAT3 activation and inflammation occurring in the entheses [38].

From the clinical perspective, one should mention that spondyloarthritis and PsA-related entheses have a primary character, while synovitis is referred to as a result of pathological process affecting the synovial lining, i.e., a secondary character [39]. The relapsing entheses may have multiple localizations, spontaneous or induced mode. On a clinical plane, enthesitis manifests itself, first and foremost, in various pain intensity and mobility limitations. While analyzing the prevalence and clinical features of entheses in > 800 PsA patients, the researchers found that the prevalence of enthesites amounted to about 35 %, the sites most often affected being Achilles tendon, plantar aponeurosis and shoulder processes [40]. The Table 1 presents the PsA-related entheseses’ prevalence. Among the risk factors associated with entheses, there are the increased body mass, younger age and high disease activity.

The enthesitis is most commonly affecting the calcaneus, namely the attachment of Achilles tendon and plantar aponeurosis to calcaneus. The soft tissue edema is most visible in the Achilles tendon, lateral process and patellar tendon under enthesitis. The entheses may not only occur simultaneously with articular lesions, but also stand out as a sole disease manifestation. About 5 % of PsA patients have such articular pathologies as enthesitis or dactylitis, standing on their own. The enthesitis symptoms are replicating various conditions, such as injuries, degenerative changes, metabolic disorders etc. It is assumed that entheses are most commonly mistaken for fibromyalgia, and thus require differential diagnostics [39].

Among all the previously explored clinical markers of PsA susceptibility, the one most frequently observed is psoriatic lesion of nail plates [41]. The character of nail modifications is characterized by an extensive range and inflammatory localization. Despite the fact that most studies differ in their description of the most commonly occurring nail plate modifications, one assumes that pitting and onycholysis are the most frequent psoriasis-attending nail lesions. The anatomical studies and imaging examinations have deepened our understanding of the nail unit and its direct association with distal interphalangeal joint [42]. The view of articular-entheseal-ungual complex as an interrelated structure emphasizes the importance of enthesal inflammatory PsA-associated changes. A similar tight structural relation accounts for the fact that the PsA patients, who are often suffering from the distal interphalangeal joint enthesis, become subject to the inflammatory nail plate modifications [41]. It allows the researchers to formulate their theory on the distal interphalangeal joint lesion probably arising due to the nail lesion and distal phalangeal enthesis [37]. Relying on the clinical and radiological findings, they claimed that psoriatic nail lesions and distal phalangeal inflammation precedes the changes of distal interphalangeal joints. This claim forms foundation for the version about the psoriasis-attending nail dystrophy may indicate the long-term distal phalan-

<table>
<thead>
<tr>
<th>Localization</th>
<th>Prevalence, %</th>
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<tr>
<td>Achilles tendon</td>
<td>76</td>
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<tr>
<td>Plantar aponeurosis</td>
<td>57</td>
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<tr>
<td>Patellar tendon</td>
<td>60</td>
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<tr>
<td>Quadriceps tendon</td>
<td>26</td>
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<tr>
<td>Greater trochanter</td>
<td>43</td>
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<tr>
<td>Lateral epicondylitis</td>
<td>19</td>
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<td>Medial epicondylitis</td>
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Table 1. PsA-related entheseses’ prevalence detected by means of ultrasound examination [43]
The enthesitis may be revealed by the clinical examination or visual imaging techniques. At the clinical examination, enthesitis manifests itself as a painful reaction upon healthcare provider’s thumb pressing the patient’s entheses (~4 kg/cm²) unless the provider’s nail tip gets white. The enthesitis may be more clearly detected by the visual imaging techniques, such as the ultrasound examination or magnetic resonance imaging (MRI). At the ultrasound examination, enthesopathy manifests itself as a muscle thickening at the bone attachment site, loss of typical layered tissue structure and appearance of minor hyperechogenic inclusions.

The measurements obtained with clinical examinations in rheumatology (OMERACT) [44] define enthesopathy as a case of abnormal hypoechogenic and/or thickened tendons or ligaments at the bone attachment site. It may be visualized at two dimensions, confirmed by a powerful Doppler signal and/or bone modification (enthesophytes, erosions and irregularities). According to this all-encompassing definition, the inflammatory modifications may be detected by a gray-scale ultrasound; they look like the membrane thickening, synovial bursa expansion or hypoechogenic tendons or ligaments. Upon examination, the dopplerography detects the intensified blood circulation. Increased vascularization is a fundamental enthesis sign according to the dopplerography. All the other gray-scale enthesis modifications (enthesophytes, erosions and calcification) are considered the chronic changes, which may also be diagnosed by the standardized X-ray.

Taking into account the fact that enthesitis is a key clinical symptom, there were clinical enthesitis measurement techniques developed, namely in case of ankylosing spondylitis. The Mander enthesis index (MEI) was the first one developed, and remains the most sensitive one [4]. In order to evaluate enthesitis by MEI, the researcher uses pressure at over 66 various enthesis sites. The patient’s reaction is registered by the 4-point score of sensitivity: 0 — no pain, 1 — light tenderness, 2 — moderate tenderness and 3 — extremely acute pain, causing the patient’s negative reaction. However, the MEI takes too long and may cause discomfort to a patient. The modern clinical medicine barely uses the MEI. The Maastricht Ankylosing Spondylitis Enthesitis Score (MASES), used in case of ankylosing spondylitis, reduced the number of engaged entheses up to 13. The PsA-modified MASES encompasses 15 enthesis sites (plus the plantar fascia added) [45]. In order to detect enthesitis, they also use the Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index (LEI), scoring 16 entheses [46], the Berlin enthesis index, scoring 12 entheses, the Leeds Enthesitis Index (LEI), scoring 6 entheses [47], as well as the minor SPARCC versions: SPARCC 8/16, scoring 8 entheses; SPARCC 6/16, scoring 6 entheses [48]. The enthesis is most commonly evaluated as 0 (no enthesitis) or 1 (present enthesis signs) for every enthesis site.

Despite a considerable progress in spondyloarthritis and PsA and introduction of new targeting drugs, there was no major randomized controlled trial (RCT) in charge of enthesitis evaluation as a final cut-off point. But for this limitation, one may obtain a wide variety of information on various therapeutic approaches from the recent clinical trials recruiting spondyloarthritis and PsA patients.

The clinical practice of enthesitis treatment is aimed at curbing inflammation and preventing the further tissue reaction, caused by inflammation. At present, all the medications used for enthesitis treatment are reducing inflammation or facilitating symptoms. The treatment of clinical enthesitis is most often relegated to the NSAID use, controlling symptoms and slowing down the new bone formation (osteoproliferation) [6]. The ultrasound examination confirms the NSAID effect on vasodilatation and inflammation of entheses sites [49]. The clinical examinations are truly demonstrating enthesitis’ higher sensitivity to the NSAIDs rather than synovitis’ sensitivity; this fact being confirmed by our understanding of PGE, leading role, associated with enthesis rather than with synovitis. The enthesis-associated NSAID effects may be realized by the inhibited transcortical and cerebral vasodilatation as well as the curbed PGE-related pain reaction. In case of an axial spondyloarthritis, the NSAIDs are used to restrict osteoproliferation and synesmophyte formation, though the data of their efficacy are not comprehensive. Unless enthesitis becomes chronic, the NSAIDs do not frequently enable the disease control, and there is a need for additional medication.

The localized glucocorticoid (GC) injections are also quite commonly used to treat peripheral enthesitis in the clinical practice; however, there is little evidence of their effectiveness. There are different clinical guidelines on injections [50], which is why most experts prefer the NSAIDs as the first-line medication for enthesitis. The localized GC injections around entheses are frequently used whenever the NSAIDs are contraindicated or failing. One should remember that in case of Achilles tendon enthesitis, the GC injections should be targeted at the retroachilles bursa, beyond Achilles tendon, in order to avoid its rupture.

As to the conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), Methotrexate (MTX) demonstrated certain effectiveness in the enthesitis treatment, though not to a similar extent as synovitis treatment. It is well-known that Methotrexate is even more effective in cases of synovial inflammation, rather than in cases of enthesal one. Similar conclusions were made on Leflunomide and Sulfasalazine (SSZ). The latter was found ineffective against the enthesal inflammation [51]. In a multicenter open Tight Control of Psoriatic Arthritis (TICOPA) RCT recruiting the PsA patients, 25.7 % of patients with enthesitis are fully recovered after 12 weeks, though mean enthesitis score changes were 0 [52]. The SEAM-PsA RCT compared Methotrexate monotherapy, Etanercept monotherapy or a combined therapy involving both medications, the early PsA patients reveal a full enthesitis resolution; within a group of Methotrexate monotherapy, this figure amounts to 43.1 % [53].
By contrast, Apremilast, which acts as a selective inhibitor of the enzyme phosphodiesterase 4 (PDE4) approved for the PsA treatment, at the moment is an only accessible per os as targeted synthetic disease-modifying antirheumatic drug (tsDMARD) with a confirmed efficacy against enthesitis. The Apremilast suppresses several cytokines being produced and taking part in an enthesal inflammation, such as the IL-17A, IL-23 and TNF [54], and curbs the neutrophil migrating to the inflammation sites. In this way, the Apremilast affects the key cytokines and cells participating in the enthesisogenesis. The combined analysis of PALACE 1-3 studies, comparing the Apremilast with placebo, ascertained that a higher rate of enthesitis patients were fully recovered after the Apremilast treatment (27.5 %) rather than after placebo (22.5 %) after 24 weeks, though this fact was not statistically confirmed. The recent long-term findings of PALACE 1-3 demonstrate that a percentage of patients achieving a full recovery after enthesis (by MASES) grows up to 55 and 62.4 % after 3 and 5 years, respectively [55]. Although these findings are promising, the Apremilast is lacking additional data to ascertain its efficacy against the peripheral entheses, as MASES focuses primarily on the axial rather than on the peripheral entheses, while other indices (such as SPARCC and LEI) consider the peripheral entheses.

The role of TNF inhibitors in the enthesitis control reflects their well-documented effectiveness in the spinal pain reduction under the spondyloarthritis and ankylosing spondylitis [56, 57]. The spinal pain resulting from an axial spondyloarthritis and ankylosing spondylitis occurs due to the fibrocartilaginous enthesal joints, such as sacroiliac joints and sites of ligament attachment at the anterior and posterior vertebral bodies, commonly associated with a significant osteitis. Furthermore, the TNF inhibitors also improve the signs and symptoms of peripheral enthesitis, such as plantar enthesitis attending the axial spondyloarthritides and peripheral enthesitis lesions [58]. At the same time, several RCTs on PsA patients bring in valuable evidence on the TNF inhibitors effectively controlling the peripheral enthesitis: after the Infliximab treatment, a number of patients with plantar enthesitis drops by 50 % in one of the studies [59]. The statistically confirmed improvement of all three enthesis indices (SPARCC, LEI and MASES) was confirmed after the Adalimumab treatment [60]. The Etanercept, Golimumab, Certolizumab have also confirmed their effectiveness in the peripheral enthesitis treatment.

There was a more significant evidence gathered on the Th17 pathways inhibitors’ effectiveness against enthesites. The Ustekinumab, which inhibits the IL-12/23 p40, demonstrated its effect in the enthesitis treatment of 47 % PsA patients with peripheral and axial lesions, compared to placebo (16 %) [61]. A recent study confirms that the Ustekinumab is effective despite a previous csDMARD use and disease duration [62]. The Guselkumab, which inhibits the IL-23 p19, also demonstrated promising results at the Phase 3 of PsA enthesis treatment trials. The combined DISCOVER-1 and DISCOVER-2 findings proved that 44.9 % and 49.6 % of patients receiving Guselkumab every 4 and 8 weeks, respectively, have a complete enthesitis resolution compared to only 29.4 % patients in the placebo group [63]. A considerable enthesis improvement emphasizes a leading role of the IL-23 – IL-17 axis in the enthesal inflammation. This concept is confirmed by the trials of IL-17A inhibitor (Secukinumab and Ixekizumab) efficacy against the PsA and ankylosing spondylitis. The use of IL-17A inhibitors improves the enthesis indices up to a complete enthesitis resolution in ~ 50 % of patients treated with Secukinumab and 30—40 % of those treated with Ixekizumab [64, 65]. Overall, an extraordinary clinical effectiveness of the IL-23 – IL-17A pathways inhibitors, and the ability of these therapeutic agents to control the axial symptoms of spondyloarthritides, ascertains the pathophysiological concept of the IL-23 – IL-17A—dependent inflammation of entheseal structures.

The modern trials reveal that an enthesis should be treated as an individual organ, as this concept enables explanation of various pathological modifications, such as bursitis, synovitis and extracapsular changes of ligament/tendon entheses affected by spondyloarthritides. The enthesitis is an important and outstanding feature of spondyloarthritides, ankylosing spondylitis and PsA; however, its management remains a complicated issue. Despite the progress in pathogenesis interpretation, imaging methods and treatment options, there are a lot of unfulfilled demands. The future studies should be focused on the detection of imaging tools, best applicable for the clinical diagnostics and objective monitoring of treatment response. Further studies are required to choose optimal medications and regimen of their use in the enthesitis patients with spondyloarthritides.

Conflicts of interests. The author declares the absence of any conflicts of interests and own financial interest that might be construed to influence the results or interpretation of the manuscript.

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Клінічне значення ентезитів при спондилоартритах: від патофізіології до лікування (огляд літератури)

Резюме. У статті наведені новітні погляди стосовно анатомії та патогенезу ентезів, клінічних особливостей, можливості діагностики та лікування. Урахування ентезів вважається критичним у діагностиці та лікуванні різних його форм. Типовими локалізаціями ентезів є місця прикріплення ахіллової сухожилки та патогенезу ентезів, клінічних особливостей, можливостей лікування. На патологічні процеси впливають функціональні взаємозв'язки тканин хребців. Структури, зосереджені в ділянці ентезів, мають місце від воронків до артритного спатакту: запалення; патогенез; лікування; огляд.

Information about author
I.Yu. Golovach, MD, PhD in medicine, professor, MBA, Honored Doctor of Ukraine, Head of the Center of rheumatology, Clinical Hospital “Feofaniya” of the Agency of State Affairs, Kyiv, Ukraine, e-mail: golovachiyu@gmail.com; phone: +38 (050) 654-21-88; https://orcid.org/0000-0002-6930-354X

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Головач И.Ю.
Клиническая больница «Феофания» Государственного управления делами, г. Киев, Украина

Клиническое значение энтезитов при спондилоартритах: от патофизиологии к лечению (обзор литературы)

Резюме. В статье представлены новейшие взгляды относительно анатомии и патогенеза энтезитов, клинических особенностей, возможностей диагностики и лечения. Поражение энтезисов считается отличительным патолого-клиническим признаком группы спондилоартритов; этот симптом включен в классификационные критерии Международной группы по изучению спондилоартритов (ASAS) для периферических и аксиальных форм. Типичными локализациями энтезитов при спондилоартрите являются: место прикрепления ахиллова сухожилия и подошвенного апоневроза к пяточной кости, латеральный мышелок плечевой кости, медиальный мышелок бедренной кости, верхний край подвздошных костей, вертелы бедренных костей, остистые отростки позвонков. Структуры, сосредоточенные в области энтезисов, имеют анатомическую, функциональную и физиологическую взаимосвязь и формируют единый синовиально-энтезиальный комплекс. В отличие от ревматоидного артрита, при котором основной патологический процесс проходит в синовиальной оболочке, при спондилоартрите основной морфологических изменений является энтезит, а развивающийся артрит (синовит) является вторичным по отношению к энтезитам. Энтезит выявляется у 30–50 % пациентов со спондилоартритами и ассоциируется с более высокой активностью, высокими показателями боли и худшим качеством жизни. Наличие энтезитов у больных псориатическим артритом ассоциируется с поражением осевых и периферических суставов, высокой вероятностью акинезирования, высокой активностью заболевания, выраженным болевым синдромом, ухудшением качества жизни и функционального состояния, нарушением сна. Кроме того, энтезит рассматривается как предвестник негативного прогноза заболевания и может предсказывать меньшую вероятность достижения ремиссии и низкую активность. Энтезиальное воспаление возникает в результате механического и/или инфекционного стресса, приводя к активации простагландина Е2 и интерлейкина-23 с последующей вазодилатацией и активацией T-клеток и врожденных лимфоидных клеток типа 3. Дальнейшее воспаление в результате активации врожденного иммунитета характеризуется высвобождением фактора некроза опухолей и интерлейкина-17, что приводит к притоку иммунных клеток, таких как полиморфноядерные нейтрофилы. Пролиферация мезенхимы под влиянием интерлейкинов-17 и -22 характеризуется активацией и пролиферацией резидентных мезенхимальных стволовых клеток наложностной капсулы. Лечебные стратегии остаются неопределенными при энтезитах. Чаще всего используют нестероидные противовоспалительные препараты, локальные инъекции глюкокортикOIDов, апремиласт, а также таргетные препараты — ингибиторы фактора некроза опухолей и интерлейкинов-17 и -23.

Ключевые слова: энтезит; спондилоартрит; псориатический артрит; синовиально-энтезиальный комплекс; простагландин Е2; воспаление; патогенез; лечение; обзор