The chronic low back pain (CLBP) is a condition severely debilitating the workability and life quality of about 13% adult population [1].

According to the recent recommendations, the CLBP is classified into 3 categories: non-specific, specific (provoked by the inflammatory, metastatic processes, or fracture) and radiculopathy-related pain. In 80–90% cases, the back pain is referred to as a non-specific. The term of “a non-specific pain” includes the presence of a specific pain substrate, subject to diagnostification; which is why diagnostic procedures are not relevant. Among the exclusion criteria, there are neurological pathologies, a high risk of metastatization, vertebral body fractures or inflammation; the effectiveness of anti-TNF-α therapy is being explored. The sporadic reference data on our disposal indicate that patients with MCs and chronic low back pain, along with instability, who do not respond to a conservative treatment, may be referred for the surgical treatment to relieve pain and improve quality of life. However, not all of the presented methods of surgical treatment with chronic back pain are effective in patients with the Modic changes. The divergence of patient treatment outcomes presented by various sources indicates the need for a further research to understand the MC pathogenesis and develop pathogenetic approaches to the treatment of this pathology.

Keywords: back pain; Modic changes; intervertebral disc; vertebral endplate
The discogenic back pain is provoked by the disc injury with no nervous structure involvement. The most debated issue is the substrate of the long-lasting pain following the disc injury. The MRI technique registered not only the intervertebral disc damage, but also the adjoining vertebral endplate damage. Among the above-mentioned factors, the degenerative disc changes combined with endplate damages are considered the key reason of the non-specific CLBP [9]. The MRI-registered changes of signal from the endplate to the vertebral body are described and classified into 3 types by Modic [10]. Further on, this classification was named the Modic changes (MCs).

The search for reference sources was performed by the PubMed, Google engines, and Elsevier information platform – ScienceDirect. The search depth was 15 years; the focus was made on the studies of the recent 5 years (67% studies). The search was performed by the following keywords: Modic, Modic changes 1, 2, 3, structural injuries, risk factors, non-specific chronic low back pain, and treatment methods.

Modic change interpretation by the MRI

The Modic changes Type 1 (MCs1) is characterized by a hypointense signal in the T1 mode, hyperintense signal in the T2 mode and hyperintense signal in the STIR mode (Fig.1). With the Modic changes Type 2 (MCs2), the hyperintense signal is registered in the T1 mode, the hyperintense signal is registered in the T2 mode and hypointense signal is registered in the STIR mode (Fig.2). The Modic changes Type 3 (MCs3) is characterized by the MRI-registered hypointense signal in the T1 mode, hypointense signal in the T2 mode and hypointense signal in the STIR mode (Fig.3).

All the three Modic change types constitute different stages of one pathological process. The period of transfer from Modic changes Type 1 to Modic changes Type 2 to Modic changes Type 3 may take several years; however, there may occur a reverse case – transformation of Modic changes Type 2 to Modic changes Type 1. About 20% injuries constitute a mixed Modic changes Type (Modic changes Type 1/2 or Modic changes Type 2/3) [11]. In a number of cases, the Modic changes Type 1 changes remain intact for a long time; however, in the rare cases this stage may be reversed. The Modic changes impact the lumbar spine at various levels, but most often they are observed at L₄/L₅ and L₅/S₁. The MCs are frequently attending the spinal segment instability. According to the metaanalysis data, the MCs prevalence in the CLBP patients accounts for 43% and only 6% subjects with MCs do not suffer from pain [12].

Histological changes

The Modic changes Type 1 are provoked by an acute inflammatory process, attended by the fibrovascular changes and subchondral bone marrow edema, adjoining the endplates [10]. The structural integrity of endplates is compromised; the usures or microfissures are formed and filled with a granulation tissue. The endplates get porous, and the PGP 9.5-immunoreactive nerve fibers occur [13]. The density of nerve endings in the porous endplates is significantly higher than in the regular ones, resulting in an intensified sensory signal and pain chronization. The endplates become a transporting system for penetration of the anti-inflammatory mediators from the disc into the bone marrow. Furthermore, the endplate cells under the MCs are expressing the tumour necrosis factor α (TNFα).

The histological changes under the Modic changes Type 2 are manifested by the adipose regeneration of bone marrow in the inter trabecular subchondral bone spaces, belonging to the endplates and penetrating the inner vertebral body [10]. This stage is considered a stable phase of degenerative disc changes with a positive conversion into the Modic changes Type 3.

The characteristic feature of the Modic changes Type 3 is the subchondral bone sclerosis, spreading to endplates.

While analyzing the microarchitectural parameters and bone remodeling indices in the biopates obtained from the patients aged 35-75 years with three types of MCs, the high-
est bone turnover has been registered in the samples of Modic changes Type 1 patients, along with the increased indices of osteoid-to-bone surface ratio and eroded surface-to-bone surface ratio, testifying to an intensified osteoblast and osteoclast activity [14]. An increased rate of active osteoclasts was found also in the MCs-adjointing regions, implying to their role in the change pathogenesis. The osteoclastogenesis activation may be attributed to the factors secreted by the degenerating IVDs. The patients with Modic changes Type 1 register an increased rate of OSCAR osteoclastogenesis gene activator, as well as statistically significant associations of M-CSF1, RANKL, RUNX1 and RUNX2 cytokine genes in charge of osteoclast differentiation and proliferation; their expression also increasing with MCs2 [15]. The MCs2 bone formation was reduced; the osteoprotegerin biosynthesis also got diminished. The MCs3 changes have been reported in line with the subchondral bone sclerosis [10]. The bone architecture has also been modified; the MCs3-associated bone trabecular thickness was higher than the one associated with MCs1 and MCs2, in terms of bone volume fraction and trabecular thickness [14].

There is a negative correlation revealed between the IVD height and MCs1 surface enlargement and a weak positive correlation revealed between the disc degeneration (by Pfirrmann) and MCs1 surface enlargement [16].

**Modic change risk factors**

It has been 33 years ago that the first description of the Modic changes Type 1 endplate disorder was published. However, the issues related to the causes underlying this pathology are as yet debated.

There are several alternative theories of MCs1 development: traumatic injury of the vertebral endplate, disc injuries related to the endplate disorders, localized effect of anti-inflammatory mediators expressed by the disintegrating disc, and infection caused by the relatively pathogenic microorganisms [10, 17-19].

**Traumatic injury of the vertebral endplate due to mechanical overload.** This is the reason Modic has indicated, pointing out an association of endplate changes with the degenerating IVDs. This association results in an increased force applied to the vertebral endplate, microinjuries and bone marrow edema. The endplate injury may be caused by dis- cectomy, chemonucleosis, spondylodesis, referred to as an accelerated disc degeneration model [10, 20]. On the other hand, the MCs1-originating endplate injuries are predictors of the quick progressing and adjoining IVD deformation. It was revealed that during one year the MCs1 results in an accelerated IVD deformation [21]. The MCs2 is predominantly associated with a hyper-strain and systemic factors.

**Degenerative disc changes and inflammatory mediators.** The intervertebral disk degeneration (IDD) is one of the most common CLBP causes. It may occur independently, or in conjunction with the MCs1, 2 or 3 [4]. In the group of IDD patients, the MCs at the lumbar spine level vary from 19 to 59 % [22]. The IVDs, cartilage endplates and bone marrow constitute a common system. Whenever there occurs a change in one component, a domino effect is initiated [23]. The nucleus pulposus cells may stimulate an anti-inflammatory cytokine release (TNF-α, IL-1β), IL-6 and IL-8), resulting in the developing MCs [24, 25]. The inflammatory cascade associated with the IVD and endplate degeneration, a concealed discitis and autoimmune reactions also provoking the MCs [26, 27].

The autoimmune theory implies an accentuated mechanical overload resulting in the IVD degeneration and a further cell autoimmune response.

**Infectious theory** of the MCs1 development is the most frequently debated [19, 28, 29]. Most studies feature strong evidence as to the MCs being a form of chronic inflammatory process, associated with a gram-positive anaerobic Propionibacterium acnes (P. Acnes / Cutibacterium acnes / C. acnes) bacterium [30, 31] present as a relatively pathogenic flora on the skin, in the mouth cavity, intestinal tract and external auditory meatus [32]. The degeneratively modified discs contain other types of bacteria, such as Coagulase-negative staphylococci epidermidis, Saprophyticus and Corynebacterium propinquum; however, P. acnes predominated to a considerable extent (45-84 %) [33].

There are two P. acnes pathways penetrating the IVDs described: via the fibrous ring crevices into the nucleus pulposus and via macrophages ingesting P. acnes and penetrating the IVDs. The P. acnes ruins the lysosomal macrophage activity, and following their demise releases the viable bacteria [30, 33]. The nucleus pulposus is a perfect site of the bacterial growth, considering the low oxygenation and absence of immune control. The bacterial metabolites and cytokines released by the disc in large quantities via the injured endplate cause an edema and inflammation of the adjoining bone marrow [28].

The P. acnes penetrating the IVDs cause apoptosis and autophagy of the nucleus pulposus cells, aggravating the disc degeneration [31]. Many researchers support the hypothesis of the P. acnes’ role in the disc degenerative changes. Similar evidence was obtained from the animal experiments [34, 35]. After the injection of P. acnes originating from the L₅ – L₆ discs of MCs1 patients into the rat tail’s discs, at the 3rd day of the experiment the researchers observed an IL-1 and IL-6
The MCs1 is mostly associated with a pronounced low back pain with the greatest intensity in the morning [45]. The pain is intensified while unbending or transfer from the horizontal into vertical position. The pain syndrome intensity is significantly correlated with MCs1-affected region [16]. The MCs-associated pain has an inflammatory character, is attended by the spinal morning stiffness occurring during an hour, though with a low rate of systemic inflammation [46, 47]. The pain syndrome intensity depends on the localization; it is higher with MCs occurring in the lower lumbar vertebral bodies (L₁/L₂, L₂/L₃) than with the ones occurring in the upper vertebral bodies (L₆/L₇, L₇/L₈) [39]. Furthermore, the MCs patients are more frequently affected by the spondylodiscitis, and have a higher rate of disc degeneration compared with patients having no MCs [46]. While transferring from Modic Type 1 to Modic Type 2, the pain intensity decreases [48]. Based on the studies of clinical manifestations, it was suggested that the CLBP patients with MCs should be considered a special category [12, 49], while the MC-attended back pain is to be converted into a separate nosology – an active discopathy [47].

Diagnostics

There is an ongoing search for markers enabling identification of the specific MC-attended CLBP features. While analyzing a high sensitivity C-reactive protein (hsCRP) blood rates of three groups of patients (MCs1, MCs2 and control group (MCs0)), the highest indices were registered in the group of MCs1 patients (4.64 mg/L for MCs1, 1.75 mg/L for MCs2 and 1.33 mg/L for MCs0) [50]. The authors consider this index to be useful for the MC diagnostics and monitoring under the CLBP, while the C-reactive protein has no information value for this category of patients [38, 50].

At present, there are no differences revealed between the inflammatory serum biomarkers (IL-1β, IL-6, IL-8 and TNF-α), oxidative-restorative status (thioles, protein oxygenation products, carbonyl groups) and collagens, i.e. cartilage degradation markers (CollⅡ-1 and CollⅡ-1N02), in the group of CLBP patients with/out MCs1 [51].

The study exploring 46 serum biomarkers (inflammatory mediators, signal molecules, growth factors and bone turnover markers) revealed only markers (IL-1sRII and hepatocyte growth factor (HGF)), which were increased in the group of patients with MCs1 and MCs2 in comparison with the control group. However, those markers did not depend on the MCs type or extent [52]. One should continue explorations in this domain.

Treatment

At presence, there is a “perfect MCs therapy” consensus [53]. It may probably be attributed to various pain generators, inconclusive response and frequently negative outcome of the conservative CLBP treatment for the MCs patients. The reference sources feature various therapy approaches: from steroidal injections directly into the intervertebral discs to antibiotics, bisphosphonates and anti-TNF- monoclonal antibodies.
**Medication**

**Antibiotics.** The issue of antibiotics use by the MCS1 patients is one of the most debatable, as it is conditioned by the presence of a multitude of various data on the role of disc infection and its association with MCS1 (see above).

The 2013 randomized blind placebo-controlled trial, involving 162 patients with CLBP, herniated IVDs and MCS1, confirmed the efficacy of antibiotics (Amoxicillin/Clavulanic acid in a dose of 500 mg/125 mg 3 times a day for 100 days) compared to the placebo by the Roland-Morris Disability Questionnaire and the Visual Analog Scale for Pain (VAS Pain). The use of antibiotics by the MCS patients is referred to as MAST (Modic antibiotic spine therapy) [54].

However, the 2019 double-blind placebo-controlled multicentric trial involving 180 patients with CLBP, herniated IVDs, MCS1 and MCS2, who were taking Amoxicillin/Clavulanic acid in a similar dose for three months, did not produce comparable results [55]. The antibiotics treatment was prescribed with no previous microbiological confirmation of the infection. The discussion on those two major studies [54, 55] is underway. The thorough expert analysis resulted in a conclusion about the unlikely negative character of Braten L.C.H. et al. [55]'s findings, as the authors did not produce any full study analysis [38].

The second randomized clinical trial (71 patients with the CLBP of over 6 months, following the intervertebral hernia excision) demonstrated the MAST efficacy (Amoxicillin/Clavulanic acid in a dose of 500 mg/125 mg 3 times a day for 100 days) according to Roland-Morris Disability Questionnaire and VAS Pain in comparison with the placebo group [56]. The positive findings were obtained for the MCS1 patients after 3 months of MAST use (Amoxicillin/Clavulanic acid in different doses: low (2 mg a day) and high (1.5 g a day during one month, and later 3 g a day during 2 months) [57]. There was no difference found between the group of low and high doses (52.9 and 53.3 %). However, in line with positive results, there is a study of recent years, which does not confirm the efficacy of antibiotics use to treat the CLBP and MCS [58].

The contradictory nature of findings may be attributed to the fact that *P. acnes* produces a biofilm, further complicating the bacterium’s detection, protecting it from the host’s immune system and antibiotics themselves [59]. In this regard, to obtain a valuable clinical result one should ascertain the MCS patient selection, singling out those more susceptible to the antibiotic response, in order to optimize the treatment outcomes and minimize its risks [38].

**Antiresorbsents.** The positive role of bisphosphonates and Denosumab was confirmed for the successful treatment of MCS [60, 61]. The study compared the effect of a single IV infusion of a 5 mg Zoledronic acid with the effect of placebo infusion, based on the profile of 39 serum biomarkers of the MCS1 and MCS1/MCS2 patients. It was also ascertained whether the blood serum biomarkers (inflammatory mediators, signal molecules, growth factors and bone turnover markers) correlate with the MC type and extent after treatment [61]. The bone remodeling markers (procollagen I intact N-terminal propeptide (iPINP) and alkaline phosphatase) were proved to decrease. The iPINP modification correlated with a reduced area of MCS1 injury. However, the pain-related rate of Interferon gamma-induced protein 10 (IP-10) grew in the group of patients treated with the Zoledronic acid; this fact found unexpected by the study authors, as the Pain VAS diminished. The painkilling effect of the Zoledronic acid and Denosumab may be associated with an osteoclast-inhibiting effect, and slowdown of the bone resorption in the CLBP patients with MCS, which is typical for this medication [60].

Anti TNF-α therapy. The TNF-α plays a pivotal role in the inflammatory process among the MCS1 patients, and the TNF-α inhibiting turns into a probable therapeutic strategy. The randomized clinical trial of Infliximab (monoclonal anti-TNF-α antibody) used to treat patients with an acute/subacute sciatica, caused by the herniated L4/L5, and L5/S1 IVD and MCS, did not reveal any differences in the pain intensity; however, the duration of pain syndrome was reduced in comparison with the placebo group after 1 year of treatment [62].

The studies of this type continue. There is a plan to perform a randomized double blind placebo-controlled multicentric trial to examine the Infliximab effect in comparison with the corticosteroid injections, and the reference data of control group CLBP patients with MCS (BackToBasic studies) [63]. In the foreseeable future, the anti-TNF-α medication may be included into the protocol of MCS patient treatment.

**Low-invasive methods.** The interdiscal corticosteroid injection produces positive results in the active discopathy patients [64]. The response to the interdiscal corticosteroid injection was assessed in the group of MCS1 patients [65-67]. Six months after the interdiscal corticosteroid injection, 64 % MCS1 patients registered a pronounced pain intensity reduction, 29 % – a moderate pain reduction by the Pain VAS and Oswestry Disability Index (ODI). With MCS2, a significant improvement was observed in 27 % patients and a moderate one – in 27 % patients [68]. In the group of CLBP patients with no MCS, only 9 % patients registered a pain intensity reduction. After the corticosteroid injections, the MCS1 patients did not experience a pain syndrome during 9 months [67]. The authors associated an absent CLBP with a “MCS1-to-MCS0” conversion. The corticosteroid injections may be considered a short-term effective alternative for patients with the discogenic CLBP and MCS in case of a non-efficient conservative therapy [69].

The efficacy of epidural steroid injections was confirmed in 70 % IDD patients with MCS1, according to the Pain VAS and Oswestry Disability Index (ODI) [70]. The authors concluded that this method of quick alleviation is effective in case of an acute aggravated discogenic pain.

The patients with CLBP of over 6 month-long and MCS1, MCS2 and MCS3, who did not respond to a conservative treatment for at least 3 months, were subject to the *nerve basivertebral* ablation at the L4, L5, L5, Ls, and S levels [71, 72]. After treatment, no patients registered any neurological condition; the pain was diminished by the VAS data, while according to the Macnab criteria, during the entire period of observation 50 % patients evaluated the treatment to...
Surgical treatment. At present, there is a wide scope of surgical methods used to treat spinal pathologies. However, the data on the outcomes of surgical MCs treatment are fragmentary, and summarized in terms of surgical MCs treatment at the lumbar spine level [73]. The outcomes of discectomy, spondylosis, and total disc endoprosthetics are analyzed, using 14 papers, 7 prospective and 7 retrospective studies that involve 1652 patients 49 % of whom had MCs [73]. There was a positive dynamics registered after the total disc endoprosthetics, no reliable evidence as to the effectiveness of spondylosis treatment (authors attribute this fact to a limited number of studies), while the discectomy produced negative outcomes. Another post-discectomy study revealed a variability of MCs1 and MCs2 activity at various stages of the observation, as well as a transformation of one MCs type into another (MCs1 into MCs2 and vice versa) [74].

The positive outcomes were obtained for 70 MCs1, MCs2 and MCs3 after the posterior spondylosis at the 6th and 12th month of observation, based on the Pain VAS and Oswestry Disability Index (ODI) [75]. While performing the contrastive analysis of posterior spondylosis and laminectomy, any positive results were confirmed only for the posterior spondylosis [76]. An effective alternative treatment method is a posterior dynamic spinal stabilization combined with MCs1 and MCs2, pronounced degenerative changes, herniated IVDs and non-stable spinal segment [22]. The study performed after the surgery (within an interval of 3, 12 and 24 months) demonstrates a significant reduction of pain intensity (by the VAS and Oswestry Disability Index (ODI)) compared with pre-surgical indices. Furthermore, the height of intervertebral space was on average considerably more significant in the post-surgery group of patients than in the pre-surgery group, after 3 and 12 months.

In order to perform a surgical treatment of MCs1 patients resistant to the conservative treatment, one should resort to the vertebral augmentation by means of bioactive resorbable bone cement [77]. 218 patients were operated on, and then became subject to a follow-up observation of 1 year. Out of those, 172 patients demonstrated positive outcomes 4 weeks after surgery, 19 % patients registered a gradual improvement during the initial 6 months. In both groups, the pain did not disappear completely; however, the patients experienced a significant improvement of their daily activity. The vertebroplasty-related complications were not revealed. The vertebroplasty may be considered as a MCs1 treatment option, in order to reduce pain and improve the life quality of patients resistant to the conservative treatment [78]. In line with the European CLBP recommendations, one should explore the efficacy of surgical methods within the framework of high-quality randomized controlled trials where the conservative treatment methods may be used for the control and monitoring purposes [79].

Conclusions

The Modic changes are most frequently registered in the group of patients with a chronic non-specific pain at the lumbar spine, in particular for the conservative treatment refractory cases. One of the key MC development mechanisms is the anti-inflammatory molecule migration from the degeneratively-modified disc into the vertebral bodies, i.e. implying a close association between MCs and disc degeneration.

There are no protocols of MCs1-related back pain treatment developed on the evidence medicine basis. Certain progress was registered with the MAST, corticosteroid and antiresorbent injections, as well as with surgical methods. The discrepancy of patient outcomes presented by various reference sources testify to the necessity of further research.

Conflicts of interests. Authors declare the absence of any conflicts of interests and their own financial interest that might be construed to influence the results or interpretation of their manuscript.

References


Зміни Modic у поперековому відділі хребта: гістологія, фактори ризику, клінічна картина і лікування

Резюме. У статті наведені дані огляду літератури, присвяченого змінам замикаючої пластинки тіла хребця, описаним М.Т. Modic (MCs), які з високою частотою визнаються в поперековому відділі хребта у пацієнтів із хронічним болем у спині. Епілог MCs невідома, найбільш імовірними сьогодні вважають три причини: механічну, інфекційну та біохімічну, загальним механізмом для всіх є міграція прозапальних молекул із дегенеративно зміненого диску. Був виявлений і описано тісний зв’язок між MCs і неспецифічним хронічним біль у спині. За дегенерації диску підвищене навантаження на замикальні пластинки може привести до мікротріщин у них, через які медіатори запалення надходять у кістковий мозок і провокують MCs. Протоколів лікування MCs із позиції доказової медицини не існує. Певні успіхи отримані при викорис-