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The State of Bone Mineral Density, Cytokine Status and Endothelial Dysfunction in the Patients with Reflex Manifestations of Lumbar Osteochondrosis and Possible Ways of Their Correction

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Abstract

More significant positive evolution of pain syndrome elimination in osteopenia-associated lumbar osteochondrosis in the case the course of meloxicam pharmacopuncture is included in the complex treatment in comparison with the group of conventional treatment (from 100% to 6.7 and 26.35%, respectively). Implication of meloxicam pharmacopuncture in the complex treatment of patients with osteopenia- associated lumbar osteochondrosis resulted in certain decrease of anti-inflammatory cytokines (necrosis factor for tumors-α and interleukin-1) as well as increase of anti-inflammatory interleukin-10 cytokine in comparison with conventional intramuscular drug injection. 3 months' conventional treatment enhanced by meloxicam pharmacopuncture revealed reliable tendency to the recovery of lost bone weight (2.46±0.04) % according to Young Adult % value) and more substantial decrease (considering NO_2 metabolite level). of endothelial dysfunction (from 5.1±0.02 to 3.8±0.05 mcmol/l, $p<0.05$), what confirmed high anti-inflammatory meloxicam efficacy as well as the practicability of its injection into acupuncture points according to the suggested technique.

Key words: reflex manifestations of lumbar osteochondrosis, osteodeficiency, pharmacopuncture, meloxicam (movalis), cytokine status, endothelial dysfunction.

The problem of lumbar osteochondrosis remains topical in the clinical neurology due to its prevalence as well as rapid progression of functional disturbances and early incapacitation of able-bodied individuals. Another serious problem is osteodeficiency since systemic decrease of bone mineral density (BMD) in forms of osteopenia and osteoporosis is found in the bulk of osteochondrosis patients. Today, the problem of combined osteoporosis and osteochondrosis that is not infrequent in elderly patients in particular, is acute, the combination aggravating the course of either disease often resulting in severe consequences.

Although a lot of theories as to osteochondrosis development and its neurologic manifestations are available, knowledge of etiology, pathogenesis, diagnostics and treatment is scarce [12]. Recently,

the development of vertebrogenic pain syndrome is more and more attributed to immunological factor. Due to new convincing evidence, osteochondrosis may be regarded not only as a major degenerative spine problem but as a nosologic form with persisting inflammation as a serious pathogenic factor [13]. Despite plenty of researches available, many aspects of lumbar osteochondrosis pathogenesis and therapy have not been adequately studied yet, the cytokine status in particular [5]. Cytokines are biologically active substances of protein origin producing both local and systemic effect on the regulation of synergistic processes between hematopoietic, nervous and immune systems [9]. As universal regulators of cellular functions, cytokines provide the linkage of immune and other systems. At pico-and nanomolar concentrations, cytokines exhibit non-enzymatic activity, their biologic effect being universal under various pathogenic factors. Cytokines content and their correlation generally represent the evolution of pathologic process and correlate with the disease activity that is indicative of therapeutic efficacy and has prognostic value [4]. According to available data, imbalanced cytokine profile occurs in lumbar osteochondrosis. The correlation of pro-and anti-inflammatory cytokines is not only indicative of the disease severity and systemic adaptive capacity in pathologic conditions but also a marker of pain syndrome treatment efficacy [9]. Activated cytokines are supposed to play an important role not only in the initiation of inflammatory process but also in the regulation of osteoclasts and osteoblasts functional activity, alongside with revealing resorptive and antiosteoporotic properties. According to some reports, impaired system of immune mediators is essential in the pathogenesis of secondary osteoporosis at the background of acute rheumatism. High anti-inflammatory cytokine levels have been found to promote systemic inflammatory response.

The role of nitrogen oxide (NO) system as a universal regulator of general biologic effect involved in the development of a number of physiologic and pathologic processes have been studied widely for the last decades [2]. NO can act as a mediator of intercellular communication of immune neuroendocrine system that interacts with cells through ordinary diffusion and as a secondary messenger, being involved in the regulation of major intracellular processes, providing cells adaptation to the changes in functioning conditions [2]. Moreover, some researchers single out NO as a separate “stress-limiting NO system” [15]. Considering the universality of mechanisms, NO is involved in both normal and pathologic states, the derangement of the system should be expected to be of significance in lumbar osteochondrosis. There is experimental evidence that NO causes numerous catabolic effects in the cartilage by stimulating inflammation and degradation of matrix metal proteinases as well as by inhibiting collagen synthesis together with proteglicans and by activating the cartilage cells apoptosis [11]. In these patients, immune stresses due to cytokine effect stimulate NO synthesis [6]. Under cytokine effect, the expression of the gene responsible for the synthesis of inducible nitrogen oxide synthetase occurs. High NO concentrations exhibit rather cytostatic (cytotoxic) than regulatory effect resulting in enhanced autoimmune manifestations [15]. Depending on the amount and production site,

NO exhibits both damaging and protective action [2]. However, the role of cytokine and NO system in the development and progression of lumbar osteochondrosis and osteodeficiency remains unclear.

Development of treatment methods for the patients with lumbar osteochondrosis is another pressing problem. Highly selective cyclo-oxygenase-2 inhibitors proved to be the most appropriate for the pain syndrome in lumbar osteochondrosis [5, 12]. Among the drugs is meloxicam (movalis) that was found to suppress cyclo-oxygenase-2-dependent synthesis of pro-inflammatory prostaglandins and to maintain cyclo-oxygenase-1-dependent synthesis of "physiological" prostaglandins. Movalis exhibits marked anti-inflammatory and analgesic action as well as high clinically confirmed tolerance and safety. Continuous meloxicam monotherapy has been found to slow down knee joint osteoarthrosis equally with glucosamine sulphate and chondroitin sulphate that relates it to the drugs with potential structural and modifying action.

The latest data indicate that some non-steroid anti-inflammatory drugs (NSAID) may effect the BMD by acting on biochemical mediators (cytokines, prostaglandins and growth factors) [6]. In consideration of the fact that the synthesis of BMD loss-linked prostaglandins mainly occurs through the mediation of cyclo-oxygenase-2, some researchers assume that by inhibiting it, the NSAID may prevent the BMD decrease [10]. Bone remodeling reveals numerous signs of inflammatory process including osteoblasts-macrophages and osteoblasts-fibroblasts interaction [7]. Recently, an alternative to conventional ways of meloxicam administration has been suggested. In particular, V.A. Shyrokov and his co-authors have proven the efficacy and safety of meloxicam administration into trigger zones in vertebrogenic lumbar ischialgic syndrome. In view of the possible effect of classical acupuncture on microcirculatory processes, immune status and reparative capacity of organs and tissues as well as analgesic action and harmonious effect on the nervous system [1, 3, 8], the authors of the study suggested the research of meloxicam pharmacopuncture to the group of patients with lumbar osteochondrosis at the background of pain syndrome.

The objective of the research is to analyze the evolution of cytokine status and the parameters of bone tissue condition as well as endothelial dysfunction syndrome in the patients with reflex manifestations of lumbar osteochondrosis and associated osteodeficiency under the influence of complex treatment including the course of conventional muscular and acupuncture meloxicam administration.

Materials and methods: 46 patients with reflex manifestations of lumbar osteochondrosis at the background of pain syndrome were examined in the outpatient departments. The classification of nervous system vertebrogenic diseases developed by I.P. Antonov (1985) was used for diagnosing. The spine damage was confirmed by radiological evidence as well as by magnetic resonance or computer tomography. The BMD was studied with two-photon X-ray densitometer Lumar DPX-A No. 2589 at the lumbar section of the spine. Standard BMD parameters of L1-L4 lumbar section and

intervertebral fissures were analyzed [1, 14]. The BMD degree was determined by T-corelation (osteopenia, osteoporosis or osteosclerosis) [7]. The values were estimated according to the WHO recommendations (Geneva, 1994) and osteopenia levels – after l.Ya. Rozhynska [14]. Neurologically, all patients had pain syndrome of varying intensity in the lumbar section of the spine evaluated in %. The cytokine content was determined with Stat Fax 303 immune enzymatic analyzer and Interleukin 1beta – IFA –BEST (IL-1) test systems, the tumor necrosis alpha-factor – with IFA –BEST (TNF-α) (Vector Best, Russia) and TGF-β – with reagents (Ukrmedservis, Ukraine). Endothelial dysfunction syndrome was studied by NO_2 metabolite level (Green method) with Griess reagent. The control group comprised 20 healthy people. All calculations were made with Mathcad 14 software. The Student's t-criterion two-sample test was used for the evaluation of average value distinction reliability.

Patients with lumbar osteochondrosis at the background of pain syndrome were divided into 2 groups. Group 1 (25 patients) were subject to conventional therapy: (selective cyclo-oxygenase-2 NSAID-inhibitor meloxicam (movalis), 15 mg (1.5 ml) intramuscularly, 1 per day No. 5, followed by oral intake (15 mg per day) No. 10, as well as chondroprotectors, biostimulants, therapeutic physical training, physiotherapeutic procedures, massage, vascular mediators and vitamins B). Group 2 (21 patients) underwent conventional therapy with meloxicam No. 5 pharmacopuncture procedures. Acupuncture points in sacrolumbar and gluteal areas with sufficient muscle layer for safe pharmacopuncture (V21-25, V50-54, V27-29, V36-40, V55-57) were used. Movalis was injected in dose of 1 ampoule per session (1.5 ml, 0.2-0.3 mg into each point with an insulin syringe) for 5 days. The correction program for Group 2 differed from that for Group 1 in the way of the drug administration only. The patients were positive as to the procedures due to rapid clinical and primarily analgesic effect, no side effects or technical problems.

Results and discussion: according to two-photon X-ray densitometry data, differently directed BMD changes were found in 137 patients with lumbar osteochondrosis (osteosclerosis – in 76 or 55.5%, BMD decrease of different degree due to osteopenia – in 46 or 33.6%, osteoporosis – in 15 or 10.9%). Simultaneous osseous tissue changes in the forms of osteoporosis and osteopenia were found in 42 (30.7%) patients with lumbar osteochondrosis that was indicative of local manifestations of lumbar osteochondrosis and systemic osteopenic changes.

The evolution of the pain syndrome was determined in the patients with osteopenia-associated lumbar osteochondrosis prior to (100% in both groups) and after the treatment course (Group 1 – 26.3%, Group 2 – 6.7%). These findings confirm more significant positive evolution of lumbar osteochondrosis-associated pain syndrome in the case the course of meloxicam pharmacopuncture is included in the conventional treatment.

Table 1 shows the data of BMD evolution in 25 patients with lumbar osteochondrosis (initial BMD level within 2d degree osteopenia) who underwent conventional treatment including traditional meloxicam administration, compared with the data in 3 months.

Table1. Evolution of BMD in osteopenia-associated lumbar osteochondrosis (n=25) under conventional treatment, the course of traditional meloxicam administration included

Bone tissue indices		L1	L2	L3	L4	L1-L4	P
Young Adult %	1	78,842± 0,892	79,083± 0,942	82,354± 0,253	80,765± 0,130	80,572± 0,736	
	2	79,354± 1,603	80,275± 1,805	83,752± 0,103*	80,052± 0,223	81,931± 0,525	>0,05
T (Young Adult)	1	-2,034± 0,007	-2,076± 0,001	-1,843± 0,001	-1,956± 0,001	-1,942± 0,001	
	2	-1,932± 0,004	-2,035± 0,003	-1,695± 0,005	-1,757± 0,009	-1,693± 0,005	>0,05
Age Matched %	1	83,164± 0,361	82,925± 0,009	86,376± 0,011	85,034± 0,330	84,080± 1,072	
	2	82,352± 1,417	84,642± 1,005	86,611± 0,029	86,650± 1,515	84,033± 0,925	>0,05
Z (Age Matched)	1	-1,523± 0,007	-1,645± 0,009	-1,313± 0,011	-1,443± 0,012	-1,427± 0,009	
	2	-1,492± 0,003	-1,542± 0,003	-1,236± 0,007	-1,205± 0,011	-1,293± 0,013	>0,05

. Notes:
1. P – reliability of group index difference prior to and after treatment
1 and 2 - Bone tissue indices prior to and after complex treatment, conventional meloxicam introduction included

The analysis revealed the tendency to bone condition stabilization in osteopenia-associated lumbar osteochondrosis, moreover – insignificant increase of BMD values (0.89+-0.90)% according to Young Adult %. However, the values obtained being statistically uncertain ($p>0.05$), the data need further specification and advanced study.

Analysis of the osseous tissue values in the group of patients with osteopenia-associated lumbar osteochondrosis (Table 2) who underwent 3 months' conventional treatment enhanced with meloxicam pharmacopuncture course, revealed certain tendency (reliability of value differentials in the groups prior to and after treatment $p<0.05$) to increased BMD that is indicative of recovering bone weight (2.46+_0.04) by Young Adult per cent index)

Thus, whereas under conventional treatment including meloxicam resulted in virtually complete stabilization or insignificant increase of the bone weight ($p<0.05$), the meloxicam

pharmacopuncture course in the complex therapy of osteopenia-associated lumbar osteochondrosis enhanced the prior therapy considerably and caused certain recovery of the lost bone weight ($p<0.05$).

The study of the treatment programs' effect on the cytokine indices were considered to be essential for the grounding of therapeutic efficacy (Table 3).

Table 2. BMD evolution in osteopenia-associated lumbar osteochondrosis under conventional treatment including meloxicam pharmacopuncture course

Bone tissue indices		*L1*	*L2*	L3	L4	L1-L4	P
Young Adult %	1	79,843± 0,793	69,082± 1,013	83,351± 0,112	79,762± 0,004	78,573± 0,140	
	2	83,355± 1,212*	73,275± 1,804*	84,753± 0,113*	80,059± 0,006*	81,934± 0,107*	<0,05
T (Young Adult)	1	-2,032± 0,009	-2,074± 0,002	-1,857± 0,003	-1,983± 0,004	-2,041± 0,001	
	2	-1,531± 0,003*	-1,835± 0,006*	-1,492± 0,005*	-1,654± 0,007*	-1,892± 0,002*	<0,05
Age Matched %	1	79,161± 0,462	69,027± 0,961	83,372± 0,011	79,036± 0,332	77,081± 0,871	
	2	82,356± 1,103*	74,648± 1,003*	84,614± 0,127*	81,059± 0,421*	80,039± 0,802*	<0,05
Z (Age Matched)	1	-2,027± 0,007	-2,248± 0,009	-1,812± 0,007	-1,946± 0,007	-2,125± 0,001	
	2	-1,492± 0,003*	-1,745± 0,004*	-1,533± 0,005*	-1,635± 0,001*	-1,894± 0,003*	<0,05

Notes:
1 and 2 groups of patients with osteopenia-associated lumbar osteochondrosis piror to and after treatment respectively;
P – reliability of indices in the groups after treatment as to pre-treatment indices.

Table 3. Evolution of cytokine status indices in patients with lumbar osteochondrosis under the effect of various treatment complexes

Cytokine status, pg/ml	Compared Groups				
	Control (n=20)	Group 1 (n=25)		Group 2 (n=21)	
		prio to treatment	after treatment	prio to treatment	after treatment
IL-1	14,39± 5,62	94,70± 18,01*	48,34± 15,41$^{*\#}$	101,13± 14,54*	47,28±10,55$^{*\#}$ p_2 <0,15
IL-10	9,50± 3,43	17,71± 1,88*	21,28± 2,46$^{*\#}$	17,58± 1,21*	23,82±1,45$^{*\#}$ p_2 <0,001
TNF-α	6,04± 1,46	34,25± 3,54*	21,08± 3,22$^{*\#}$	39,75± 2,13*	23,38±2,68$^{*\#}$ p_2 <0,001
TGF-β	10,96± 3,99	54,55± 4,61*	89,29± 4,20$^{*\#}$	54,78± 2,29*	86,18±2,60$^{*\#}$ p_2 <0,005

Notes:
* - reliable difference as to control group, $p < 0.001$;
$^{\#}$ - reliability of the particular group's index differences prior to and after treatment, $p_1 < 0.001$;
P_2 - reliability of after treatment index differences in Group 2 as to Group 1

The treatment course in groups 1 and 2 was found to reduce IL-1 values by 50 and 54% in comparison with initial level, TGF-α – by 39 and 43%, whereas IL-10 values increased by 15 and 25% and TGF-β – by 39 and 37%, respectively. The obtained data confirmed the presence of reliably higher efficacy level ($p<0.05$) of the complex treatment with meloxicam physiotherapeutic course included on the studied parameters of cytokine status (except for TGF-β).

Lumbar osteochondrosis was found to be associated with enhanced endothelial dysfunction (considering NO_2 metabolite level). The comparative analysis of the effect of studied therapeutic programs revealed the decrease of endothelial dysfunction (considering NO_2 metabolite level) from 4.9±0.03 to 4.3±0.04 mcmol/l (in control group – 3.82±0.09), whereas meloxicam pharmacopuncture course provided more substantial effect – the decrease of endothelial dysfunction from 5.1±0.02 to 3.8± mcmol/l ($p<0.05$), what confirmed high anti-inflammatory meloxicam efficacy as well as the practicability of its injection into acupuncture points according to the suggested technique.

Summary: 1. Inclusion of the meloxicam pharmacopuncture to the complex treatment was established to provide more significant positive evolution of the pain syndrome elimination in osteopenia-associated lumbar osteochondrosis in comparison with the group of conventional treatment (from100% to 6.7 and 26.35%, respectively).

2. Implication of meloxicam pharmacopuncture in the complex treatment of patients with osteopenia-associated lumbar osteochondrosis resulted in certain decrease of anti-inflammatory cytokines (necrosis factor for tumors-α and interleukin-1) as well as increase of anti-inflammatory interleukin-10 cytokine in comparison with conventional intramuscular drug injection.

3. 3 months' conventional treatment enhanced by meloxicam pharmacopuncture revealed reliable tendency to the recovery of lost bone weight (2.46±0.04) % according to Young Adult % value).

4. Meloxicam pharmacopuncture course provided more substantial decrease of endothelial dysfunction (from 5.1±0.02 to 3.8±0.05 mcmol/l, $p<0.05$), what confirmed high anti-inflammatory meloxicam efficacy as well as the practicability of its injection into acupuncture points according to the suggested technique.

Further perspective: development of new lumbar osteochondrosis treatment techniques seems to be expedient together with pathogenic substantiation of reflexotherapy implication in the complex treatment of such patients.

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