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CORRELATION OF ANXIETY AND CHRONIC PAIN TO GRADE OF SYNOVITIS IN PATIENTS WITH KNEE OSTEOARTHRITIS

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SUMMARY

Background: *This study was conducted with the objective of finding out the correlation between synovial inflammation measured histopathologically and subjective symptoms; anxiety and chronic pain, in knee osteoarthritis (OA).*

Subjects and methods: *Thirty patients were included in the study. Ten of them were in a control group with meniscal injury, ten had early OA and 10 had late OA. Knee radiographs were graded using Kellgren-Lawrence classification. Synovial biopsies were taken during surgery or arthroscopy and synovitis score was measured by Krenns method. Anxiety was measured with Beck Anxiety Inventory and pain was taken as part of the WOMAC score (The Western Ontario and McMaster Universities Arthritis Index).*

Results: *Krenn synovitis score was determined as: no synovitis, low-grade synovitis and high-grade synovitis. Group with low-grade synovitis had significantly higher pain score than high-grade synovitis group (p=0.011). No-synovitis group had significantly lower Beck Anxiety Inventory than low-grade synovitis group (p=0.014) and high-grade synovitis (p=0.008). There are no significant differences between low-grade synovitis and high-grade synovitis in anxiety score (p=0.912).*

Conclusions: *Chronic pain is more present in late osteoarthritis, when synovitis is less pronounced. Anxiety affects patients who suffer osteoarthritis, but it is statistically the same regarding synovitis grade, i.e. whether it is early or late osteoarthritis.*

Key words: *anxiety – pain – osteoarthritis - synovitis*

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INTRODUCTION

Anxiety is an unpleasant feeling of uneasiness and worry, often accompanied with neurotic behavior and somatic complaints as an overreaction to a situation that is only subjectively seen as a menace (Seligman et al. 2007). Anxiety can be distinguished from fear, which is an appropriate cognitive and emotional response to a perceived threat, defined as short lived, present focused, geared towards a specific threat, and facilitating escape from threat. Anxiety, on the other hand, is the expectation of future threat, defined as long-acting, future focused, broadly focused towards a diffuse threat, and promoting excessive caution while approaching a potential threat that interferes with constructive coping (Sylvers et al. 2011). In one sentence, it can be defined as a fear or nervousness about what might happen (Sharma et al. 2016). Besides emotional effects of anxiety (nightmares, irritability, restlessness etc.), somatic symptoms of anxiety may also be present (neurological, digestive, respiratory, cardiac, etc.) (Testa et al. 2013).

Osteoarthritis (OA) is highly prevalent and painful disabling disease, especially among older adults. The major pathological changes include cartilage damage, the formation of osteophytes, subchondral bone sclerosis, inflammation of the synovium, degeneration of ligaments and the menisci, and alteration of the joint capsule. These changes can lead to significant pain and disability and create a substantial individual, societal, and economic burden. OA is now the most prevalent cause of chronic pain in elderly (Loeser et al. 2012, Berenbaum 2013). Current management largely emphasizes on alleviating symptoms and improving function, but for many patients these measures do not provide adequate symptom relief (Walsh & Stocks 2017, Creamer 2000). Variability in symptoms and outcomes among individuals with OA cannot be explained by the disease pathology alone. It is still unclear if pain in OA is predominantly due to inflammation or to mechanical stimulus to denuded bone due to cartilage loss (Berenbaum 2013). In last decade, with the detection of high levels of inflammatory factors in synovial fluid, it has been proposed that OA is an inflammatory disease (Robinson et al. 2016, Sokolove & Lepus 2013, Benito et al. 2005). In recent studies, it has been seen that synovial membrane elicits abundant quantities of inflammatory factors (Felson et al. 2016, Hugle & Geurts 2017, Ostojic et al. 2016). Thus, synovial inflammation has much more significance in early phase of the disease, as a result of joint instability and initial cartilage lesions (Guermazi et al. 2014). Pain is the major symptom of OA and it is still unclear what is the origin of it. If the pain is derived from the inflammatory factors and their activity on pain receptors, then it should be more pronounced during early OA, while there is a plethora of ongoing inflammatory processes

in synovium, producing abundant quantities of inflammatory factors (Sokolove & Lepus 2013). If the pain is simply mechanical stimuli of nerve endings in denuded subchondral bone, it should be more pronounced in late OA, when the cartilage is almost entirely lost (Creamer 2000, Loeser et al. 2012).

Anxiety is highly prevalent among adults in general population and more frequently found among adults with any form of painful disabling arthritis (Sharma et al. 2016). Study by Castano et al. showed that 25% of 1258 patients with OA, reported anxiety (Castano Carou et al. 2015). In the study by Axford at al. they found that among 54 patients with OA, prevalence of anxiety and/or depression was 40.7% (Axford et al. 2010). Meta-analysis showed that anxiety and depression coexist in 20% of the patients with OA (Stubbs et al. 2016). 70% of patients diagnosed with those comorbidities suffer from chronic pain (Tan et al. 2015). While management of somatic symptoms in long-term conditions has gained much impetus over last years, anxiety, depression and chronic pain remain under-detected and often under-treated in those conditions (Tan et al. 2015). Studies examining relationship between anxiety and pain in OA have generally found positive correlation. Study by Marks found higher pain scores in patients that experienced anxiety compared with those who had no such history (Marks 2015). In another study by Marks it was found that patients with a history of anxiety before operation tend to recover slower compared with those without this condition (Marks 2009). Review of 38 studies examined the impact of anxiety and depression on OA symptoms. Most studies focused on lower extremity OA (hip and knee), with one study examining hand OA patients. Diagnosis was based on clinical presentation and radiographs. Patients from the entire spectrum of disease severity were studied. Prevalence of anxiety and depression was related to index joint pain, pain at multiple sites, pain intensity, and OA severity (Sharma et al. 2016). Anxiety and fear-avoidance are associated with lower self-report scores for knee OA (Scopaz et al. 2009). In order to maximize rehabilitation for total hip or total knee arthroplasty, psychological symptoms caused by chronic pain should be treated if they are over threshold (Caracciolo & Giaquinto 2005). Studies reported that anxiety and depression increased general practitioner visits (Buszewicz et al. 2006), drug prescriptions (Blagestad et al. 2016) and post-surgical pain (Wylde et al. 2012).

So far, no study correlated anxiety to the synovitis grade in OA. Since, from current literature, we found out that pain is the leading OA symptom causing psychological disorders, the aim of the study is to correlate pain and anxiety with synovitis as the leading driving segment of joint inflammation in OA.

SUBJECTS AND METHODS

This is an analytic, observational, cross sectional study performed in University Hospital Mostar.

Patients

Study included 30 patients admitted to the Department of Orthopaedics and traumatology of University Hospital Mostar. This is a continuation of a study performed by the same authors with introduction of the psychological component - anxiety (Ostojic et al. 2016). The control group was ten younger age patients (16-40 years) admitted for fresh meniscal injury without arthroscopically visible hyaline cartilage damage, graded 0 or 1 by International Cartilage Repair Society classification (ICRS) (Brittberg & Winalski 2003). Group of patients with OA was divided by radiological, Kellgren-Lawrence (K-L) classification into two subgroups, 10 patients with mild and 10 patients with severe form of the disease (Kellgren & Lawrence 1957). Patients in OA groups were over 40 years old and had primary OA. The inclusion/exclusion criteria was in accordance with the "American College of Rheumatology Diagnostic and Therapeutic Criteria" for knee OA (Altman et al. 1986). Demographic information such as gender, age, body mass index (BMI), range of motion (ROM), knee axis, symptoms duration (in months) and clinical stage of the disease by Western Ontario and McMaster Universities Arthritis Index (WOMAC) were obtained. There is a significantly higher proportion of women in low-grade synovitis group (Table 1). Low-grade synovitis group has significantly higher K-L index than high-grade synovitis group. Other correlations have no statistical differences (Table 2). WOMAC is a clinical scale that measures pain, stiffness and quality of daily physical functions (McConnell et al. 2001). Beck Anxiety Inventory (BAI) was used for examining main symptoms of anxiety such as unusual physical symptoms, feelings and clinical signs (Beck et al. 1988). The Ethics Committee of the School of Medicine, University of Mostar and the University Hospital Mostar, Bosnia and Herzegovina approved the study and all patients gave written, informed consent. The study conforms to the provisions of the Declaration of Helsinki in 1995.

Synovial tissue collection

Larger samples of synovial tissues were taken during total knee prosthesis implantation from ten patients with advanced OA (stage 3 and stage 4 according to K-L classification). In all operations, standard medial parapatellar exposure was performed. Synovial biopsies in control group were performed arthroscopically. Samples were taken from ten patients with early OA (stage 1 and stage 2 according to K-L classification) and from control group. All patients in early OA group had their biopsies taken from medial and lateral gutters, and suprapatellar pouch, by direct visualization of the hypertrophied and inflamed tissue. Samples from control group were taken in the same manner. Standard arthroscopic knee portals were used for arthroscopy.

Table 1. Sex differences according Krenn synovitis score

	Sex				χ^2	P
	Male		Female			
	N	%	N	%		
Synovits Krenn					9.690	0.005*
No synovitis	7	70.0	2	30.0		
Low-grade	0	0.0	6	100.0		
High-grade	4	28.6	10	71.4		

*Fisher test

Table 2. Correlation between clinical parameters and Krenn synovitis score

	Synovits Krenn				U	p
	Low-grade		High-grade			
	M	IR	M	IR		
BMI	31.15	2.8	28.55	6.0	32.0	0.409
Symptom duration (years)	7.50	15.3	4.00	19.5	27.5	0.225
WOMAC	58.50	11	50.00	28	30.0	0.322
K-L index	3.50	1	1.00	2	12.0	0.009

U = Mann-Whitney U test; M = Median; IR = Interquartile range

Tissue samples were treated in the previous study and this is a procedure used (Ostojic et al. 2016). Synovial biopsies were formalin-fixed, paraffin-embedded, serially sectioned (4 μm), mounted on glass slides and analyzed using an Olympus CX41 light microscope (Olympus, Tokyo, Japan). Every 10th section underwent haematoxylin and eosin staining followed by grading according to the three synovial membrane features of Krenn synovitis score: synovial lining cell layer thickness (intima), subintima cell density (resident cells) and inflammatory infiltrate (non-resident cells in subintima), the ranking of alterations being on a scale from none (0), slight (1) and moderate (2) to strong (3). The values of the parameters were summarized and interpreted as follows: 0-1, no synovitis; 2-4, low-grade synovitis; and 5-9, high-grade synovitis (Krenn et al. 2006).

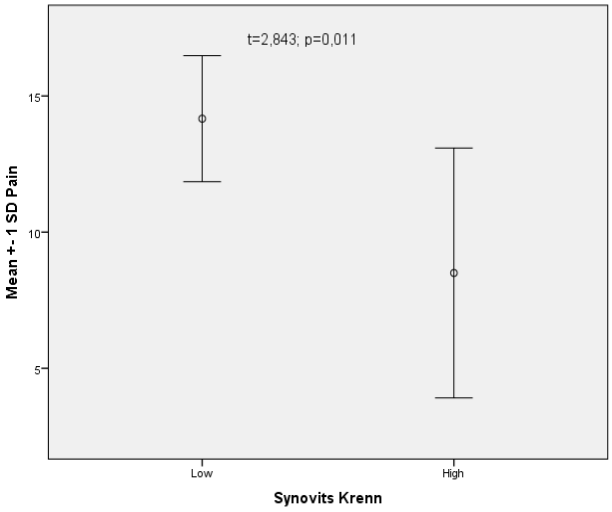

Figure 1. Correlation between pain score and Krenn synovitis score

RESULTS

Statistically significant differences were observed in pain intensivity between groups with low-grade synovitis and high-grade synovitis. Low grade synovitis has higher pain intensivity (p=0.011; Sheffe post hoc test) (Figure 1).

Differences in BAI between Krenn synovitis grade groups. No-synovitis group has significantly lower BAI than low-grade synovitis group (p=0.014; Sheffe post hoc test) and high-grade synovitis (p=0.008; Sheffe post hoc test). There were no significant differences between low-grade synovitis and high-grade synovitis (p=0.912; Sheffe post hoc test) (Figure 2).

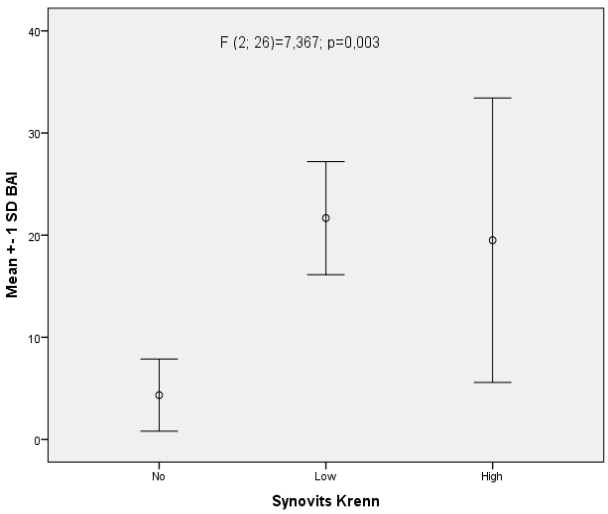

Figure 2. Correlation between Beck Anxiety inventory and Krenn synovitis score

DISCUSSION

In results that we obtained in this study, group with high-grade synovitis had statistically significant lower pain results than low-grade synovitis patients. According to these results, it can be concluded that, in late OA,

pain stimulus is more derived from nerve endings in denuded subchondral bone, than through inflammatory factors led by synovitis in early OA. In our previous study, group of patients with early OA had significantly higher grade of Krenn synovitis score than group with advanced OA (Ostojic et al. 2016), meaning that Krenn synovitis score is inversely proportional with radiologic grade of disease (K-L score). Lately, a lot of scientific emphasis has been put on proving that OA is an inflammatory disease, but also, we cannot put aside the fact that it is a degenerative condition with pronounced mechanical, wear and tear etiology (Berenbaum 2013). Subchondral bone is rich with bare nerve endings, sensitive to frictional and compressive forces that happen continuously in weight-bearing joints. Due to the fact that control group was formed of young patients with fresh meniscal injury, their knees were painful due to other reasons, so we did not include them in our pain comparison. It is evident that group with no OA nor synovitis would be considered pain-free in everyday life. Having more female patients in low-grade synovitis group might have made some statistical impact on pain score, making low-grade synovitis group more pain sensitive, which is in line with studies that show females have lower pain enduring capacity (Fillingim et al. 2009).

Looking at the comparison of anxiety level and Krenn synovitis score, we can see that patients from control group (young, active athletes) had no anxiety in everyday life, even though the questionnaire was taken after the acute injury, while both groups with synovitis, i.e. with OA, had certain level of anxiety. There was no statistical difference in anxiety level between low and high-synovitis groups. Even though there were more female patients in a high-synovitis group and females are more prone to anxiety, no statistical difference occurred (Seligman et al. 2007). There are many different explanations for these results. Out of anamnestic data, following facts were observed. Patients diagnosed with high-grade synovitis, who usually suffer from early OA, experience anxiety due to following causes. They encountered health problem that they didn't confront before, so it causes them certain level of fear of unknown. It also usually affects their work ability, since this is group of mean age of 56 years, still professionally active, who are unable to perform their professional practice. Third parameter of great importance is chronic pain due to inflammation, which is very hard for patients to endure, because it is not only present during activity, it is often felt during rest or sleep. On the other side, patients diagnosed with low-grade synovitis, who suffer from late OA, have other elements that cause anxiety. They are suffering from a degenerative, progressive disease that will lead them to an inevitable surgical procedure. This leads to feeling of fear and uneasiness. This group of patients has mean age of 72 years and many of them are dependent on others which leads them to feel defenseless and vulnerable. Many of patients with advanced OA have suffered chronic pain for years and they explain their everyday life as miserable.

Still, in clinical practice on orthopedic departments, anxiety and chronic pain remain under-detected and under-treated in degenerative conditions such as OA. Including some anxiety questionnaire like BAI would help us determine the affected patients and consulting psychiatrist would be of benefit to the patients, especially at the time before surgery. Since patients with a history of anxiety before operation tend to recover slower, it would be beneficial to treat them in time and fasten their recovery (Marks 2009). During the hospital stay, chronic pain has been well treated. Physicians should put more emphasis on treating OA pain through outpatient clinic, prescribing personalized medication for individual patients.

CONCLUSIONS

Pain is more pronounced in late osteoarthritis, with synovitis score lower. Lower synovitis score means late osteoarthritis. Anxiety affects patients who suffer osteoarthritis, but it is statistically the same regarding synovitis grade i.e. whether it is early or late osteoarthritis.

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Conflict of interest : None to declare.

Contribution of individual authors:

Marko Ostojic, Mirjana Ostojic and Violeta Soljic made substantial contributions to the conception and design of the study, acquisition of data, and analysis and interpretation of data, drafting the article and revising it critically.

Jerko Prlic revised critically the article and gave substantial ideas and suggestions.

Marko Ostojic approved the final version submitted.

Marko Ostojic (marko.ostojic@ymail.com) in the name of all co-authors takes responsibility for the integrity of the work as a whole, from inception to finished article. Hereby, we confirm that all authors have read and approved the final submitted manuscript.

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