

Evaluation of Relationship between Serum Levels of Inflammatory Factors and Clinical Symptoms in Females with Knee Osteoarthritis

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ABSTRACT

Background and Objectives: Osteoarthritis (OS) is the most common type of arthritis and joint disease, especially in women. Proinflammatory cytokines, biochemical factors, specially matrix metalloproteinases, and reactive oxygen species play important roles in joint destruction in this disease. Therefore, the present study aimed to evaluate level of inflammatory factors and its relationship with clinical symptoms of OS in female patients.

Methods: The study was performed on female patients with knee OS, referring to healthcare centers of Tabriz University of Medical Sciences. After measuring the weight and height of patients, clinical symptoms such as severity of pain and physical performance were evaluated using the Knee Injury and Osteopaedic Outcome Score questionnaire. Serum levels of IL-1 β , TNF- α , and hs-CRP in fasting blood samples were measured using ELISA kits and immunoturbidimetric assays.

Results: There was a significant association between level of IL-1 β and score of pain. There was no significant relationship between the clinical symptoms and level of other inflammatory factors.

Conclusion: The results of the present study showed that the increase in inflammatory factors is correlated with severity of pain in OS patients.

Keywords: Osteoarthritis Knee, Female, Inflammatory Markers.

INTRODUCTION

Osteoarthritis (OS) is the most common cause of human arthritis and joint disease. Lifestyle changes and increase in population of elderly people in developed and developing countries have increased the prevalence of OS (1). Symptoms of OS include joint pain and stiffness, bone erosion and decreased joint movement in knees, hips, hands, and vertebral joints, which can cause chronic pain and severe disability in patients. Since knee is a weight-bearing joint exposed to direct traumas, it has the highest prevalence of OS (2). OS is more common among women, and its incidence increases with age (3). In western countries, the prevalence of OS is 2% in people aged <45 years, 35% in people aged 45-64 years, and 68% in people aged >65 years (4). There are several risk factors for OS, including genetic factors, age, obesity, gender, high mechanical stress, etc. (5). In addition to mechanical stress, proinflammatory cytokines, biochemical factors (especially matrix metalloproteins), and reactive oxygen species are involved in joint destruction (6). Proinflammatory cytokines, particularly IL-1 β and TNF- α inhibit synthesis of matrix components such as collagen and proteoglycans (7). Animal and cell culture studies have indicated that proinflammatory cytokines produced in joints and chondrocytes play an important role in cartilage degeneration (8). Therefore, decrease in serum levels of these cytokines is the primary goal of therapeutic approaches. Proinflammatory cytokines also upregulate the expression of matrix metalloproteinases (MMPs) (9, 10). MMPs are proteolytic enzymes able to degrade extracellular matrix components (11). Level of acute phase proteins correlates with systemic inflammation and is increased in people with OS, leading to decreased cartilage volume, disease progression and aggravated clinical symptoms (12).

Joint stiffness and pain are common symptoms of OS (13). Among the tools used to study the clinical symptoms of OS, Knee Injury and Osteopaedic Outcome Score (WOMAC) has been used more frequently. Considering the increasing prevalence of OS in the world and the importance of inflammatory factors, we determined serum level of inflammatory markers in females with knee OS and evaluated its relationship with clinical symptoms of OS.

MATERIAL AND METHODS

The study was approved by the Ethics Committee of Tabriz University of Medical Sciences (code No 92127), and registered on irct.ir (Code: IRCT201311231197N17).

In this empirical trial, fasting blood samples were taken from 90 female patients (aged 40-70 years) with knee OS who were referred to the rheumatoid center of Sina hospital. Serum levels of IL-1 β , TNF- α , and high-sensitivity C-reactive protein (hs-CRP) were evaluated. The participants had mild primary bilateral knee OS based on the American College of Rheumatology criteria and body mass index of 25-35 Kg/m² (14). The people with active synovitis, secondary OS, any type of neurological disease involving muscle receptors, uncontrolled hypertension, diabetes, cardiovascular insufficiency, chronic nephrogenic insufficiency, hepatic functional insufficiency and history of consuming of furosemide, probenecid, anti-coagulants, hydantoin, sulfonamides, methotrexate, lithium salts, beta blockers, muscle-relaxing agents, and smoking were excluded from the study. Then, the serum level of markers was determined by ELISA, and the relationship between the level of factors and the disease severity was assessed. Before and after the intervention, the WOMAC questionnaire was used to evaluate clinical symptoms including pain, stiffness, and physical functionality (15). Serum high-sensitivity CRP (hs-CRP) levels were measured using a wide-range latex-enhanced immunoturbidimetric assay kit (Biosystems, Spain) (16). The CRP present in blood samples form complexes with latex-fixed anti-CRP polyclonal antibody, resulting in turbidity. The resulting turbidity has a direct correlation with the amount of CRP present in serum samples and was measured at wavelength of 500 nm using an auto-analyzer. Serum levels of IL-1 β were measured by ELISA kits (Zelbio Co., Germany) according to the manufacturer's instructions. The results were analyzed by an ELISA microplate reader (Awareness, USA), and the concentrations were calculated.

Data were analyzed using SPSS (version 16). The Kolmogorov-Smirnov test was used to examine data distribution. Normally distributed data were presented as mean \pm standard deviation (SD), while non-normally distributed data were presented as median. Qualitative data were presented as frequency

and percentage. To determine the relationship between the quantitative data, the Pearson's correlation coefficient was used for normal data and Spearman's correlation coefficient was used for non-normal data. P-values less than 0.05 were considered as statistically significant.

RESULTS

Among the participants, 50 (56.2%) were menopausal and 39 (43.8%) were non-menopausal. In addition, 75 women (84.3%) were housekeepers and 14 (15.7%) were employed (Table 1).

Table 1- Characteristics and clinical symptoms of women with knee OS (n=89)

Variable	Mean ± SD
Age (years)	52.31±6.28
Duration of disease (years)	5.28±5.19
Height (cm)	155.10±6.74
Weight (Kg)	77.06±9.95
Body mass index (Kg/m ²)	31.98±3.12
Severity of symptoms	
Total grade (0-96)	52.31±6.28
Pain (0-20)	5.28±5.19
Stiffness (0-8)	155.10±6.74
Physical functionality (0-68)	77.06±9.95

Table 2- Level of inflammatory markers in serum of women with knee OS (n=89)

Variable	Mean ± SD
IL-1β (pg/ml)	9.82±1.48
TNF-α (pg/ml)	9.81±7.04
hs-CRP (mg/L)	3.05±2.15

Table 3- The relationship between serum levels of inflammatory factor and grade of clinical symptoms in women with knee OS (n=89)

Inflammatory factor	IL-1β (pg/ml)		TNF-α (pg/ml)		hs-CRP (mg/L)	
	r	P	r	P	r	P
Grade of clinical symptoms						
Total grade	0.084	0.43	0.018	0.87	0.024	0.82
Pain	0.233	0.02	0.023	0.82	0.016	0.88
Stiffness	0.148	0.16	0.090	0.40	0.099	.036
Physical functionality	0.002	0.98	0.003	0.97	0.014	0.90

Moreover, there were positive correlations between inflammatory markers and severity of clinical symptoms in the participants (Tables 2 and 3).

DISCUSSION

OS is a chronic disease often accompanied by inflammatory signs and symptoms including pain, stiffness, and swelling leading to decreased physical functionality (16). Pain is the first and commonest symptom of OS and the main reason for visiting a physician. In addition to pain, joint stiffness and limitation of daily activities are among the important clinical symptoms in early stages of OS. Therefore, the most important goal of OS treatments is to reduce these symptoms and improve physical functionality (17). In the present study, we evaluated the clinical symptoms of the participants with OS using the WOMAC questionnaire. The total grade of symptoms in the subjects was 42.94±15.38.

The grade of pain, stiffness, and physical sub-sections were 9.21±4.55, 2.77±1.47, and 30.95±10.94, respectively. Our results are in line with the results of Malek Mahdavi et al. (18). The role of different inflammatory factors in OS etiology and pathogenesis has been studied. It has been suggested that pro-inflammatory cytokines such as IL-1β and TNF-α that are produced in active synovitis and chondrocytes, play an important role in OS pathogenesis. These cytokines can lead to production of catabolic enzymes such as MMPs, which are responsible for further cartilage matrix degeneration in patients with OS (19, 20). These cytokines also activate other inflammatory intermediates such as

cyclooxygenase 2, which in turn, increase prostaglandin E2 and joint pain inflammation (20). Furthermore, it has been shown that circulatory levels of CRP increase in OS as a marker of systemic inflammation, correlating with severity of synovial inflammation, clinical and radiological findings and disease progression (21-23). The mean level of serum IL-1 β was 9.82 \pm 1.48 pg/ml, which is similar to the results of a previous study on Iranian patients with knee OS (24). However, the serum level of IL-1 β was lower than that in two other studies on patients with knee OS in Egypt (18.5 \pm 1.6 pg/ml) and Iran (19.12 \pm 2.69 pg/ml) (25, 26). The mean serum level of TNF- α and hs-CRP in the patients studied was 9.71 \pm 7.04 pg/ml and 3.05 \pm 2.15 mg/L, respectively. These values were similar to other studies on OS patients in Iran (3.02 \pm 2.11) (24), United States (3.4 \pm 4.7 mg/L) (27) and Netherland (28). The difference in the level of inflammatory factors in different studies could be due to the differences in disease severity, type of drugs and supplementations used, ethnicity and analytical methods. We found a significant correlation between serum levels of IL-1 β and

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grade of pain. However, we found no significant correlation between serum levels of IL-1 β and total grade, stiffness, and physical functionality. In addition, there was no significant correlation between serum levels of TNF- α and grade of clinical symptoms. Moreover, serum level of hs-CRP had no significant correlation with grade of clinical symptoms. These results are consistent with study of Imamura et al. (29), which reported no significant correlation between serum levels of TNF- α and grade of clinical symptoms including pain, stiffness, and physical functionality.

CONCLUSION

The results of the present study showed that increase in inflammatory factors is correlated with severity of pain in OS patients.

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CONFLICT OF INTEREST

We have no conflict of interest to declare.

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