

Post-Traumatic Arthritis: The Role of Cytokine Levels in Serum and Synovial Fluid

Naser Sarafan¹, Mohammad Fakoor¹, Abdolhossein Mehdinasab¹, Mohammad Bahadoram^{1,2},
Damoan Ashtary-Larky^{3,4}, Hossein Mahdavi¹ & Fatemeh Javanmardi⁵

¹ Department of Orthopedic Surgery & Trauma Research Center, School of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, IR Iran

² Medical Student Research Committee, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, IR Iran

³ Department of Clinical Biochemistry, School of Medicine, Ahvaz Jundishapur University of Medical sciences, Ahvaz, Iran

⁴ Health Research Institute, Diabetes Research Center, Ahvaz Jundishapur University of Medical sciences, Ahvaz, Iran

⁵ Department of Biostatistics, School of Health, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.

Correspondence: Hossein Mahdavi, Department of Orthopedic Surgery & Trauma Research Center, School of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran. E-mail: Mahdavi-h@ajums.ac.ir

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Abstract

Background and Objectives: Inflammatory processes play an important role in intra-articular fractures. The present study aimed to examine the relationship between chemerin, high-sensitivity C-reactive protein (hs-CRP), and Interleukin 17 (IL-17) serum and synovial fluid levels of osteoarthritis patients and individuals with intra-articular fractures.

Method: In this case-control study, all osteoarthritis patients and individuals with intra-articular fractures who visited the Imam Khomeini Orthopedic Clinic of Ahvaz were examined. Blood samples (5 cc) were collected prior to surgery to measure chemerin Interleukin 17, and hs-CRP serum levels. Synovial fluid samples (2 cc) were collected during the surgery.

Results: Measuring the levels of IL-17, chemerin and hs-CRP indicated a significant statistical difference between the serum and synovial fluids of osteoarthritis patients, individuals with intra-articular fractures, and the control group ($p < .001$). Post-hoc analyses showed statistically significant differences in all conditions except for hs-CRP levels between osteoarthritis patients and individuals with intra-articular fractures.

Conclusion: Discovering ways to stop or slow down osteoarthritis is a matter of great concern. The findings on osteoarthritis indicate diverse, complex, and multidimensional processes involving cytokines. Information on cytokines that effect diseases can help develop efficient therapy methods.

Keywords: intra-articular fractures, osteoarthritis, interleukin 17, chemerin, high-sensitivity c-reactive protein, serum, synovial fluid

1. Introduction

Adult intra-articular fractures of the distal radius include a distinct set of fractures which are related to post-traumatic arthritis and difficult to manage (Wojdasiewicz et al., 2014). Intra-articular fractures of the femur distal end pose difficult surgical challenges. In such cases, recovery is difficult and surgery is advised for desirable outcomes (Lieberthal et al., 2015). Intra-articular fractures of the distal end of the femur and proximal tibia are mainly caused by low-energy stumbling in elderly osteopenia patients. These fractures are signs of morbidity and usually require surgery (Hill et al., 2014). Distal radius fractures, on the other hand, are the most common type of fractures among individuals under 75 years old. To improve functionality and avoid long-term disability, treatments should be based on the patients' personal characteristics (Loi et al., 2016).

Inflammatory processes play an important role in the recovery of intra-articular fractures. From a molecular perspective, the recovery process is carried out by three kinds of signaling factors: inflammatory cytokines,

Transforming Growth Factor-beta (TGF- β), and other growth and angiogenic factors (Gerstenfeld et al., 2003; Bahney et al., 2015). IL-1, IL-6, and TNF- α that signal the beginning of recovery processes, have been identified as important members of the first group (Gibon et al., 2016; Loi et al., 2016). These factors are not only produced by macrophages and inflammatory cells, but also by mesenchymal cells in the periosteoma. They also have a central role in down-stream responses to injuries by chemotactically influencing inflammatory factors, resulting in the stimulation of extracellular matrix synthesis and angiogenesis. Moreover, they cause the fibrogenic function of cells outside the injury area (Loi et al., 2016). The expression of these factors reaches its climax 24 hours after the fracture, ends in the cartilage production phase and increases again during remodeling (Chubinskaya & Wimmer 2013; Loi et al., 2016). On the other hand, severe articular trauma can cause osteoarthritis. One study estimated about 21 million Americans to have osteoarthritis symptoms, 12% of whom had post-trauma arthritis due to post-trauma etiology (Vaananen et al., 2014).

Osteoarthritis is an articular disease in which inflammatory and cartilage-destructive mediators are released into the synovial fluid from articular tissues (Kapoor et al., 2011). It is known that osteoarthritis is followed by the destruction of the subchondral bone cartilage and the remodeling and inflammation of the synovial membrane; however, its etiology and the factors triggering it are less studied. Inflammations caused by articular trauma may bring about other articular diseases. Following articular injury, the level of inflammatory cytokines in the synovial fluid increases. Previous studies reported levels of Interleukin 1 and TNF- α to have reached their climax 24 hours after injury (Hui et al., 2012; Lieberthal et al., 2015). These levels remain high for weeks and even months after trauma (Catterall et al., 2010; Olson et al., 2014; Christiansen et al., 2015). Based on clinical observations, cartilage derived biomarkers increase significantly a month after knee injury (Kramer et al., 2011; Konttinen et al., 2012). This shows that significant cartilage damage takes place weeks after the trauma, hence early intervention can effectively prevent long-term articular destruction (Imamura et al., 2015). Previous research has shown that cytokines other than IL-1 and TNF, might be involved in osteoarthritis and can thus be considered for recovery purposes (Haseeb & Haqqi, 2013). Researchers of pathogenesis osteoarthritis have showed interest in the IL-17 family, a cytokine group with inflammatory effects that includes six members acting through five receptors (Pawlowska et al., 2009; Fahy et al., 2015). Main articular cells affected by IL-17 are chondrocytes and FLSs which express the IL-17 receptor (Lubberts et al., 2000).

Chemerin is a passive (18 kDa) chemo-attractant adipokine activated by posttranslational C-terminal cleavage (Luangsay et al., 2009; Inci et al., 2016). In-vitro chemerin exogenous stimulates angiogenesis through cell proliferation, endothelial migration, and capillary tube formation which are all basic stages of angiogenesis development (Vermi, Riboldi et al., 2005). It is worth mentioning that chondrocytes express chemerin and its receptors and that IL-1 β can increase the chemerin expression rate (Sharif et al., 2000; Jiang; 2013; Greene & Loeser, 2015).

The present study was carried out to find the effect of inflammatory factors such as hs-CRP, IL-17, and chemerin on osteoarthritis and articular fractures to identify other potential factors affecting these fractures, and to compare healthy individuals with those experiencing intra-articular fractures.

2. Method

2.1 Design and Participants

This study was conducted on 60 patients with osteoarthritis, intra-articular fractures and healthy persons. All osteoarthritis patients or individuals affected by intra-articular fractures who visited Imam Khomeyni Orthopedics Clinic, Ahvaz, Iran, participated in this case-control study. Patient eligibility was confirmed by the hospitals orthopedists. Ethical considerations were addressed by following the guidelines of the Ethical Committee of the Ahvaz University of Medical Sciences and obtaining the patients' written consent prior to the study.

2.2 Inclusion Criteria

All participants had to be above 40, have endured knee pain for at least three months, and show degenerative M.R.I. symptoms. Evaluations were also carried out during surgery.

2.3 Exclusion Criteria

Patients with prior knee surgery or a history of knee-joint injuries caused by exercise or trauma as well as those who were taking anti-inflammatory drugs (e.g., Corticosteroids), those showing inflammation-related symptoms, diseases of the immune system or joints warm symptoms were excluded from the study.

2.4 Data Collection

Full details of the study were explained to participants who had all undergone knee-joint surgery as part of their

therapy. Synovial fluid was collected under the supervision of orthopedists who took all required precautions to prevent common infections that occur during surgery or subsequent therapy. Participants were later interviewed and a questionnaire was given to them to collect general information regarding their age, gender, physical activity, smoking habits, dietary supplements and drugs (such as antioxidants or fish-oil taken more than 1 gr per day), weight-loss diets, medical history and diabetes. Blood samples (5 cc) were collected prior to surgery to measure serum levels of Chemerin, Interleukin 17, and high-sensitivity C-reactive protein. Synovial fluid samples (2 cc) were also collected during the surgery. Immediately after each step, blood samples were centrifuged in 3000 g for 5 minutes to extract the serum which was then kept in 80 °C until next usage. Heparinized synovial fluid (SF) samples were obtained from subjects. All samples were stored frozen at -80 8C until analysis. ELISA (Enzyme-Linked Immunoassay) was used to determine plasma and synovial fluid levels.

2.5 Statistical Analysis

Categorical data were reported by frequency and percentage and quantitative continuous data was indicated by mean ±SD. A one-way ANOVA was performed to compare three groups, also post-hoc Tukey test was utilized for investigating differences the control and test groups. Additionally, chi square analyses and ANOVA were performed to assess if the group matched in demographic variables. Statistical analyses were performed by using SPSS18 software (SPSS Inc., Chicago, IL, USA.). P - values less than 0.05 were considered as the level of significance.

3. Results

3.1 IL-17

As figure 1 shows, the amount of serum IL-17 was significantly different from the synovial fluid IL-17 for the osteoarthritis, intra-articular fracture, and control groups (p < .001). The one way ANOVA showed that sample type (fluid), group, and sample type-group interactions had a significant effect on IL-17 (p < .001). Tukey post-hoc tests indicated a significant difference between the osteoarthritis and the control groups (p < .001), the intra-articular fracture and the control groups (p < .05), and the osteoarthritis and intra-articular fracture groups (p < .001). Also there was no significant difference between demographic characteristic (e.g. age and gender) of study participants in three intervention groups (Table 1).

Table 1. Baseline characteristics of study participants in different groups

Groups Variables	Intra-Articular	Osteoarthritis	Control	P Value
Age	34.5±7.02	36.3±9.34	32.5±10.35	0.26
Gender	Male	9(45%)	8(40%)	0.71
	Female	11(55%)	12(60%)	

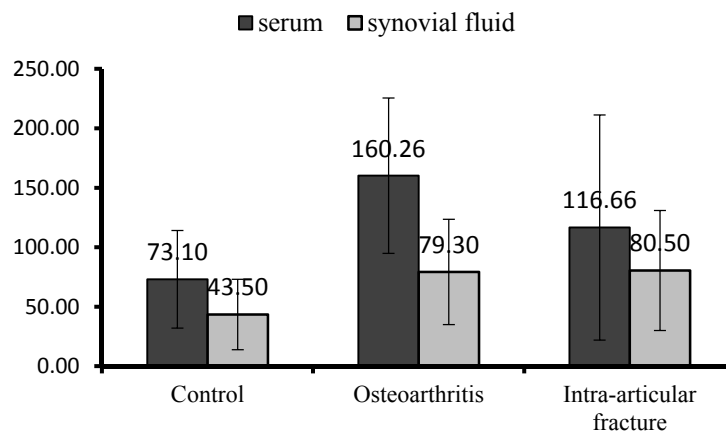


Figure 1. Comparison of the three groups for Interleukin 17. Mean values for synovial fluid and serum were 80.56 ± 50.4 and 116.66 ± 94.7 for the intra-articular fracture group (p < .001). For the osteoarthritis group, the mean values for synovial fluid and serum were 79.38 ± 44.3 and 160.26 ± 65.3, respectively (p < .001). Regarding the control group, the mean values for synovial fluid and serum were 43.58 ± 29.6 and 73.1 ± 41.08, respectively (p < .001)

3.2. Chemerin

As indicated by Figure 2, serum chemerin was significantly different from synovial fluid chemerin for the osteoarthritis, intra-articular fracture, and control groups ($p < .001$). The ANOVA showed that sample type (fluid), group, and sample type-group interactions significantly affected chemerin ($p < .001$). Tukey post-hoc tests indicated a significant difference between the osteoarthritis and the control groups ($p < .001$) and the intra-articular fracture and the control groups ($p < .001$). The osteoarthritis and intra-articular fracture groups, however, did not show any significant difference ($p > .05$).

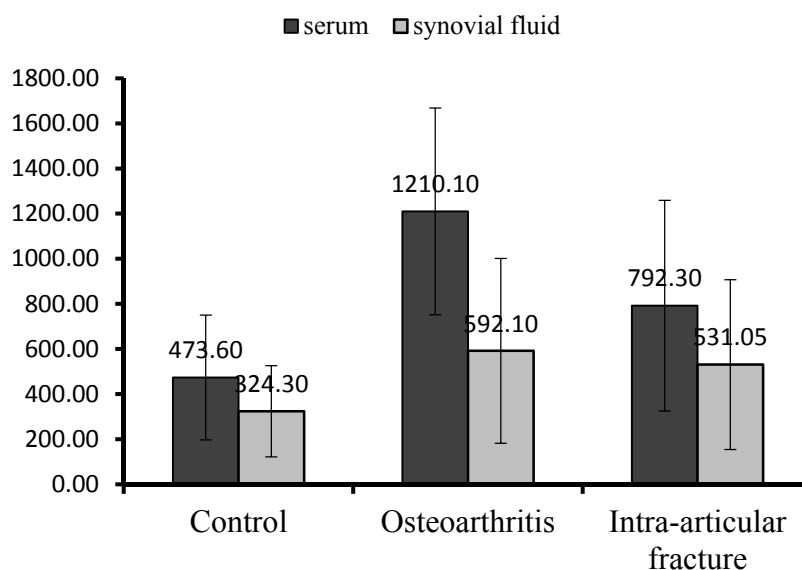


Figure 2. Comparison of the three groups for chemerin. Regarding the intra-articular fracture group, the mean values for synovial fluid and serum were 531.05 ± 376.36 and 792.31 ± 466.7 , respectively ($p < .001$). For the osteoarthritis group, the mean values for synovial fluid and serum were 592.09 ± 409.8 and 1210.10 ± 458.2 , respectively ($p < .001$). AS for the control group, the mean values for synovial fluid and serum were 324.39 ± 202.1 and 473.63 ± 276.9 , respectively ($p < .001$).

3.3. Hs-CRP

As figure 3 indicates, serum Hs-CRP was significantly different from that of the synovial fluid for all three groups ($p < .001$). The ANOVA showed that sample type (fluid), group, and sample type-group interactions had a significant effect on Hs-CRP ($p < .001$). Tukey post-hoc tests indicated a significant difference between the osteoarthritis and the control groups ($p < .001$) and the intra-articular fracture and the control groups ($p < .001$). The osteoarthritis and intra-articular fracture groups did not show any significant difference ($p > .05$).

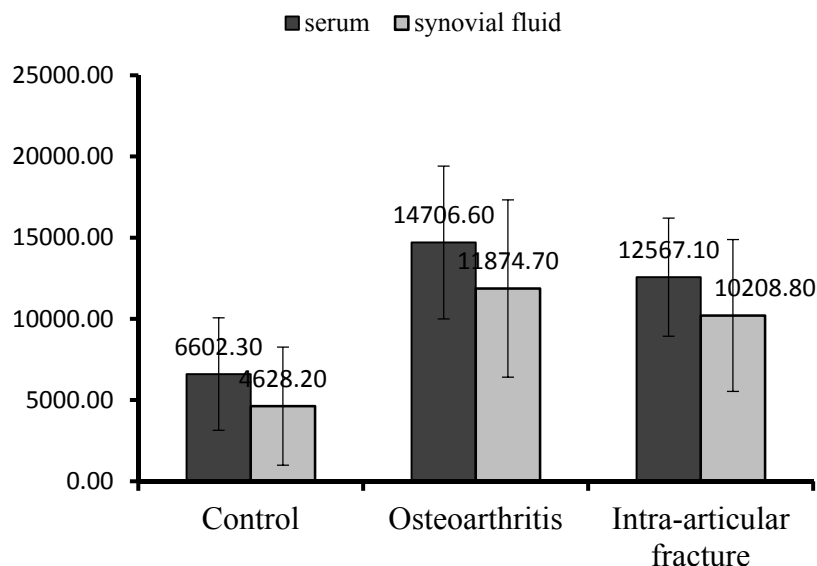


Figure 3. Comparison of the three groups for Hs-CRP. Regarding the intra-articular fracture group, the mean values for synovial fluid and serum were 8903.95 ± 5538.2 and 11292.02 ± 5217.5 , respectively ($p < .001$). For the osteoarthritis group, the mean values for synovial fluid and serum were 1187.74 ± 5461.1 and 14706.65 ± 4708.1 , respectively ($p < .001$). As for the control group, the mean values for synovial fluid and serum were 4628.21 ± 3637.2 and 6602.30 ± 3465.1 , respectively ($p < .001$)

4. Discussion

The present study aimed at investigating the differences between serum and synovial fluid levels for chemerin factors, high-sensitivity C-reactive protein, and IL-17 in osteoarthritis patients and individuals with intra-articular fractures. The results indicated significant statistical differences between chemerin levels, high-sensitivity C-reactive protein, and IL-17 in serum and synovial fluids of osteoarthritis patients, intra-articular fracture patients, and healthy individuals.

Osteoarthritis is one of the most common chronic diseases in middle-age and elderly populations (Ruiz-Romero & Blanco, 2010). The specific pathogen that causes osteoarthritis is still unknown, but it is thought to be related to trauma, strains, and the immune system responses. Biological aspects affecting cytokines in the synovial fluid and the articular cartilage have recently been studied due to the fact that Cytokines are important factors for treating and preventing osteoarthritis (Kapoor et al., 2011). IL-17 has also been widely researched on pathogens and the treatment of multiple sclerosis (Kallaur et al., 2013; Elain et al., 2014; Sexton et al., 2014), systemic lupus erythematosus (Onishi & Gaffen, 2010; Tanasescu et al., 2010), inflammatory bowel disease (Yu et al., 2012; Katz et al., 2014), and psoriasis (Raychaudhuri, 2013; Chiricozzi, 2014). Nevertheless, its relationship with osteoarthritis needs to be studied further.

The IL-17 family plays an important role in autoimmune diseases, hence the precise regulation of this cytokine can prevent inflammation. Previous research has shown that inflammatory responses in T-cells, epithelial, endothelial, and fibroblasts may affect the expression of IL-17, which can in turn, regulate chronic inflammations and host defenses causing tissue injury and autoimmune effects (Singh et al., 2014; Reinert-Hartwall, Honkanen et al., 2015). Many studies have shown that this cytokine is pre-expressed in rheumatoid arthritis (RA) patients. IL-17 can destroy collagen and weaken the bones in-vitro (Tanabe & Yamashita, 2014; Roeleveld & Koenders, 2015). Such neutralization of this cytokine or its receptors was shown to decrease arthritis symptoms in a rat model. IL-17 deficiency was also shown to protect the host against arthritis-related collagen damage in a rat model, and IL-17 gene therapy was shown to intensify it (van Baarsen et al., 2014; Zheng et al., 2014). It can be concluded, therefore, that IL-17 in RA patients might cause both inflammation and bone-destruction. This cytokine can also help improve cartilages, synovial cells, macrophages, and osteocytes, which can, in turn, result in the production of inflammatory cytokines (e.g., TNF-A, IL-1b). IL-17 can also stimulate several chemokines which cause neutrophil, macrophage, and lymphocyte aggregation in synovial membranes, ultimately resulting in severe articular injury (Hu et al., 2014; Wojdasiewicz et al., 2014).

The present study found a direct relationship between the level of IL-17 in the synovial fluid of patients with osteoarthritis and articular fractures. Based on this finding, this cytokine might be considered as a new potential biomarker used to diagnose increased osteoarthritis side effects.

Yang et al., studied the existence of auto-antibodies against IL-17 and their relationship with disease activity in 60 RA patients, 72 osteoarthritis patients and 61 healthy individuals. Their findings indicated that antibody increase in response to IL-17 was directly related to the disease activity of those patients. Such evidence suggests that antibodies against IL-17 may play a protective role against the pathogens of such diseases (Yang et al., 2015). Liu et al., studied the role of IL-17 levels in the synovial fluid and its relationship with knee-arthritis intensity. They concluded that IL-17 might play an important role in osteoarthritis pathogens and controlling it can, therefore, delay osteoarthritis pain (Liu et al., 2015).

Chemerin includes pre-inflammatory mediators whose role has been studied in joint inflammation and cartilage destruction in-vitro. Most studies regarding the presence of this substance in the synovial fluid have focused on the role of their pathogens. The findings of the present study suggest a statistically significant difference between serum level and synovial fluid chemerin in osteoarthritis patients, individuals with intra-articular fractures, and healthy individuals. Huang et al. studied the relationship between serum and synovial fluid chemerin levels in 124 knee-arthritis patients and 76 healthy individuals. They concluded that chemerin level may have a role in the pathophysiology and disease progression (Huang et al., 2012).

Proteolytic enzymes have been shown to activate chemerin. These enzymes increase if inflammation occurs. Chemerin belongs to an extensive adipokine family. These kinases are mediators identified as cartilage-destructive pathogens (Zhuo et al., 2012). Valcamonica et al., studied synovial fluids chemerin levels in patients with different articular diseases including osteoarthritis, RA, and psoriatic arthritis. Their study suggests similar synovial fluid and serum chemerin levels the three diseases (Valcamonica et al., 2014). The present study, however, found statistically significant differences between synovial fluid and serum chemerin levels for the three groups – osteoarthritis patients, individuals with intra-articular fractures, and healthy individuals.

Chemerin is also a chemotactic agonist considered to be a ligand for ChemR23 which is expressed on macrophages and dendritic cells. By activating FLSs through attachment to ChemR23, chemerin plays the role of a pathogen in RA (Herenius et al., 2013) and osteoarthritis (Mariani and Roncucci 2015) patients.

Evidence shows that osteoarthritis progression is accompanied by inflammation. Although hs-CRP is an index of systemic inflammation that increases in osteoarthritis patients, research findings show contradictory results. Jin et al., went through a systematic literature review and conducted a meta-analysis to study the relationship between serum hs-CRP levels and osteoarthritis. They found that low-grade systemic inflammation may play a more prominent role compared to radiography changes of osteoarthritis symptoms (Jin et al., 2015). Another study by Smith et al., showed that in addition to its role in inflammation mechanisms resulting in osteoarthritis progression, hs-CRP can be considered as a variable that can predict this disease.

5. Conclusion

Presently, researchers are looking for ways to block or slow down the progression of osteoarthritis. To this aim, certain methods are used to infiltrate intracellular transport routes that play a vital role in the inflammation processes. Research on inflammatory and anti-inflammatory cytokines is still in progress. Findings related to osteoarthritis indicate diverse, complex, and multidimensional processes at work that involve cytokines. Such information can help researchers develop efficient methods to deal with this disease.

Authors' Contribution

All authors passed four criteria for authorship contribution based on recommendations of the International Committee of Medical Journal Editors. Naser Sarafan, Mohammad Fakoor and Abdolhossein Mehdi nasab designed the protocol. Mohammad Bahadoram, Hossein Mahdavi and Damoon Ashtary-Larky developed the protocol and performed it. Critical revision of the manuscript for important intellectual content was performed by Mohammad Bahadoram. Analysis of data was performed by Fatemeh Javanmardi.

Ethical Issues

This study was approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences, (Approved ethical code: IR.AJUMS.REC.1394.35).

Conflict of Interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

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