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Article

Relationships between Serum Interleukin-6, Radiographic Severity and WOMAC Index in Patients with Primary Knee Osteoarthritis

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Abstract: Background: Osteoarthritis is the most common degenerative joint disease resulting in pain and altered joint function. **Objective:** We investigated the possible association between serum interleukin-6 and symptoms of knee osteoarthritis with regard to pain, stiffness, physical function, assessed by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). We also examined the connections between serum interleukin-6 and radiographic severity in primary knee osteoarthritis patients. **Methods:** In this case-control study, fifty primary knee osteoarthritis patients and fifty age and sex matched controls were randomly recruited. Serum interleukin-6 levels were immunoassayed in patients' and controls' serum. Patients' knee pain, stiffness and physical function were assessed by the respective subscales of the WOMAC Index. Standing anteroposterior radiographs of the knee joint were performed and graded with the Kellegren-Lawrence grade. **Results:** The mean serum IL-6 level was significantly higher in osteoarthritis patients (110.22 ± 46.98pg/ml) than controls (46.04 ± 12.34 pg/ml) (p=0.001). The WOMAC Index in patients ranged from 0–95 and the Kellegren-Lawrence score mean was 2.7 ± 0.76. There was a significant correlation between serum IL-6 levels and pain (r=0.595 p=0.001), physical function score (r=0.666, p=0.001)), and the radiographic score (r=0.799, p=0.001). Regression analysis showed that IL-6 level had a greater impact on both the WOMAC Index (p=0.005) and the Kellegren-Lawrence score (p=0.01). **Conclusion:** Serum IL-6 level is increased in primary knee osteoarthritis patients. Also, serum interlukin-6 is significantly related to osteoarthritis symptoms and radiographic severity.

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Keywords: interleukin-6; primary knee osteoarthritis; visual analogue scale; Western Ontario and McMaster Universities Osteoarthritis Index; WOMAC; Kellegren-Lawrence score

1. Introduction

Osteoarthritis (OA) is a progressive degenerative joint disease with a growing impact due to an increase in life expectancy [1]. OA affects all joint tissues, resulting in loss of articular cartilage mass, subchondral bone remodelling, new bone formation and inflammation of the synovium [2]. Knee osteoarthritis (KOA) is considered the most common type of arthritis leading to pain and dysfunction, especially in elderly population [3].

Multiple causes are involved in the development of OA including genetic predisposition, obesity, aging, and trauma [2]. Inflammation has a key role in OA pathogenesis, as inflammatory cytokines are released and this has an immediate consequence on degeneration of cartilage mass [4]. Other factors, such as damage-associated molecular mechanisms along with mitochondrial dysfunction, initiate synovial inflammation [5]. Multiple publications are focusing on the rising role of the cytokine network in OA pathogenesis [6].

Proinflammatory cytokines are considered essential players in OA, and in many other inflammatory processes [7]. In tissues subjected to high mechanical load, cytokines disturb the catabolic and anabolic processes. Among the multiple cytokines, a great importance is attributed to Interlukin-1β, tumor necrosis factor α, interleukin-6 (IL-6), IL-15, IL-17, and IL-18 [8].

Interleukin-6 is a pleiotropic inflammatory cytokine consisting of 184 amino-acids residues [9]. In OA, the synovium produces IL-6 via plasma cells or activated synovial fibroblasts in the synovial lining, while the infrapatellar fat pad (IFP) serves as an important source of IL-6 [10]. Multiple studies report catabolic effects of IL-6 on cartilage and synovium with concomitant muscular degeneration, after traumatic events. High IL-6 serum level was found to be an independent predictor of incident radiographic knee OA [11].

The above-mentioned degenerative changes are associated with pain and other OA symptoms that can lead to limitations in activities of daily living, reduced quality of life and functional impairment [12]. Hence, in-depth investigation into the commonest pathogenic factors may contribute to advancements in therapeutic targets for OA [13]. The aim of this case-control study was to investigate the possible association between serum IL-6 and symptoms of KOA such as pain, stiffness and physical function as assessed by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and to examine the connection between serum IL-6 and radiographic severity in primary KOA patients.

2. Methods

Fifty patients from the outpatient clinic of "Physical Medicine, Rheumatology and Rehabilitation Department at Tanta University hospitals" that fulfilled the American college of rheumatology classification criteria for primary KOA [14] were recruited into this case-control study. Patients and controls were excluded if they had any of the following: (1) presence of any concomitant autoimmune, inflammatory, metabolic or infectious disease; (2) secondary OA.

A control group of fifty randomly chosen healthy subjects of matched age, sex and body mass index (BMI) were also enrolled in this study. The study was approved by the Local Research Ethical Committee of Tanta University (approval code 35105/12/21). Prior to inclusion, the participants gave an informed consent. The study conforms to the provisions of the 1995 Declaration of Helsinki.

The data obtained were full medical history, body mass index (BMI), pain severity assessment using the visual analogue scale (VAS), as well as laboratory investigations including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP), serum uric acid for exclusion of secondary OA and Serum IL6.

Serum IL6 levels were immunoassayed using commercial ELISA kit supplied by Sunred Biological Technology Co., Ltd. Shanghai, China. Color changes were examined by detecting the absorbance at wavelength (450 nm) (Stat Fax 2,100, NY, USA).

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Patients' knee pain, stiffness and physical function were assessed by the respective subscales of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) [15]. The WOMAC is a broadly validated self-reported outcome measure for knee OA. It consists of 24 items divided into 3 subscales: pain (5 items), stiffness (2 items) and physical function (17 items), with each item scored on a 5-point Likert scale (none, mild, moderate, severe, and extreme). For the pain and physical function subscale, these scores were transformed to a 0 to 100 score (0 = no symptoms, 100 = extreme symptoms) with higher scores indicating more pain and more disability.

Standing anteroposterior radiographs of the knee joint were taken and graded with the Kellegren-Lawrence grade tool [16]. Kellegren-Lawrence (KL) grades were measured as: 0 = no radiographic features of osteoarthritis; 1 = possible joint space narrowing and osteophyte formation; 2 = definite osteophyte formation with possible joint space narrowing; 3 = multiple osteophytes, definite joint space narrowing, sclerosis and possible bony deformity; 4 = large osteophytes, marked joint space narrowing, severe sclerosis and definite bone deformity.

Statistical analysis was carried out using the statistical package for social sciences software, version 20.0. Data of patients were expressed as mean ± standard deviation or median (minimum–maximum) for continuous variables and as number (%) for categorical variables. Comparisons between groups for categorical variables were assessed using Chi-square test (Fisher or Monte Carlo). Student t-test and Mann Whitney test were used to compare two groups for normally and abnormally distributed quantitative variables respectively. Spearman's correlation coefficient and logistic regression analysis were considered. Significance was considered at $p < 0.05$.

3. Results

The patients' mean age was 53.86 ± 5.83 years and the mean disease duration was 5.25 ± 2.7 years. There were no significant differences between cases and control subjects regarding mean age, sex and BMI (Table 1). The WOMAC score in patients' group ranged between 0–95 and in control group it was 0-1. The KL score mean was 2.7 ± 0.76 in the patients' group. There were significant correlations between serum IL-6 and the VAS pain score, ESR levels, WOMAC score, and KL score (Table 2). Linear regression analysis revealed that serum IL-6 levels had the greatest impact on WOMAC and KL scores amongst those parameters (Table 3).

Table 1. Comparison of the demographic features, scores, laboratory investigations and interleukin-6 in primary KOA patients and control.

		Cases	Control	t. test	p. value
Sex	Male (%)	11 (22%)	16 (32%)	X2: 1.286	0.260
	Female (%)	39 (78%)	34 (68%)		
Age	Range	40 – 66	40 – 64	1.149	0.254
	Mean ± S.D	53.86 ± 5.83	52.56 ± 4.48		
VAS	Range	1 – 8	1 – 2	15.79 1	**0.001**
	Mean ± S.D	5.52 ± 1.83	1.30 ± 0.46		
BMI	Range	19 – 29	19 – 27	1.643	0.104
	Mean ± S.D	24.10 ± 2.62	23.22 ± 2.74		
WOMAC	Range	0 – 95	0 – 1	15.76 4	**0.001**
	Mean ± S.D	33.32 ± 14.91	0.08 ± 0.27		
KL grade	Grade I	14%	-	-	-
	Grade II	46%	-		
	Grade III	36%	-		
	Grade IV	4%	-		
ESR	Range	15 – 70	10 – 25	6.286	**0.001**
	Mean ± S.D	27.64 ± 10.47	17.48 ± 4.57		
CRP	Range	1 – 2.5	0 – 2	2.499	0.014
	Mean ± S.D	1.49 ± 0.44	1.27 ± 0.42		

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IL – 6	Range	39 – 320	28 – 88	9.343	**0.001**
	Mean ± S.D	110.22 ± 46.98	46.04 ± 12.34		

VAS: visual analogue scale, BMI: body mass index, WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index, ESR: erythrocyte sedimentation rate, CRP: c-reactive protein, IL-6: interleukin 6. Bold values are significant at ≤0.05.

Table 2. Correlation of serum IL-6 with age, disease duration, body mass index, visual analogue scale, Western Ontario and McMaster Universities Osteoarthritis Index, erythrocyte sedimentation rate, C-reactive protein and Kellegren-Lawrence score in primary KOA patients.

	IL – 6	
	r	P value
Age	-0.134	0.353
Disease duration	0.142	0.327
VAS	0.595	**0.001**
BMI	-0.017	0.904
WOMAC	0.666	**0.001**
ESR	0.548	**0.001**
CRP	0.109	0.452
KL score	0.799	**0.001**

IL-6: interleukin 6, VAS: visual analogue scale, BMI: body mass index, WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index, ESR: erythrocyte sedimentation rate, CRP: c-reactive protein, KL: Kellgren-Lawrence score. Bold values are significant at ≤0.05.

Table 3. Linear regression analysis for parameters most influenced by serum interleukin-6 in primary KOA patients.

	OR (95% CI)	P value
VAS	0.512 (0.298 – 1.253)	0.103
WOMAC	0.628 (0.326 – 0.854)	**0.005**
ESR	0.859(0.574 – 2.138)	0.148
KL score	0.476 (0.198 – 0.749)	**0.001**

VAS: visual analogue scale, WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index, ESR: erythrocyte sedimentation, KL: Kellegren-Lawrence score. Bold values are significant at ≤0.05.

4. Discussion

Inflammatory mediators in the serum and synovial fluid are thought to directly affect cartilage metabolism and inflammation and may constitute significant targets for the treatment of pain [2]. IL-1β, IL-6 and TNF-α have higher expression in the early stages of KOA and correlate with pain, indicating that targeting inflammation may be more efficient in alleviating pain in the early stage [17]. Given the increasingly recognized implication of synovial and subchondral inflammation in patients with primary OA, this study investigated the possible association between serum IL-6, symptoms of KOA (pain, stiffness, physical function), and radiographic severity in this group of patients. It showed that KOA patients had higher levels of serum IL-6 compared to healthy controls, and this result is consistent with earlier studies [18,19]. Accumulating evidence showed that inflammation and chronic synovitis are significant contributing factors in OA progression [2–4]. Increased levels of IL-6 in serum or synovial fluid in OA patients correlate with disease incidence and severity, while IL-6 plays a key role in cartilage pathology, e.g., via induction of matrix-degrading enzymes [20]. In the current study, serum IL-6 levels were also correlated with pain intensity assessed by VAS score. Similarly, other authors reported statistically significant associations between synovial fluid pro-inflammatory biomarkers (IL-6, IL-8) and knee pain [21,22].

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Pro-inflammatory cytokines play more than one role in the generation of pain in primary knee OA. Upregulation of IL-6 production by chondrocytes has detrimental consequences in the downregulation of collagen synthesis via matrix metalloproteinases, resulting in cartilage lesions, an important source of pain [23,24]. Aside from structural damage, pro-inflammatory cytokines may also contribute to pain through peripheral and central sensitisation, mediated by C fibres [25]. However, in a recent study, Tocilizumab, an IL-6 monoclonal antibody, was not found superior to placebo in patients with hand OA, indicating that other factors might contribute to the complex phenomenon of OA [26]. Apart from synovitis, the presence of bone-marrow lesions, erosions and bone attrition are potential sources of nociceptive pain in hand OA [26].

Serum IL-6 levels were also correlated with the WOMAC scores. A former study, reported that IL-6 in the synovial fluid is significantly associated with knee pain based on the WOMAC score [27]. In contrast, others reported that IL-6 levels have no correlation with the WOMAC pain score [28]. Inflammatory cytokines mediate pain at rest and with movement. In the context of OA, pain on movement is often more severe than pain at rest, correlates inversely with physical function, and has an earlier onset than rest pain in disease course [29].

Multiple factors contribute to physical function impairment in OA patients. Low grade chronic inflammation leads to OA-related sarcopenia which does not only target the neighbouring muscles of affected joints but can also involve all the skeletal muscles [30,31]. On the other hand, individual factors associated to OA, such as lack of physical activity and obesity can play an indirect role in the pathogenesis of OA-related sarcopenia [32]. Similarly, an inverse correlation has been observed between muscular resistance of hamstrings and serum IL-6 levels in elderly women with OA suggesting an important role for IL-6 in OA sarcopenia. [33].

In the current study, higher levels of serum IL-6 were associated with radiographic severity and higher KL grade. Similarly, a previous study showed that individuals were more likely to be diagnosed as having confirmed radiographic KOA if they had a higher BMI and increased circulating levels of IL-6 [34]. Also sex and genders are important on the late-stage KOA [35]. Other authors positively correlated synovial fluid and serum IL-6 with the intensity of lesions in x-ray imaging [22]. All this may have interesting consequences on the therapeutic approach [36]. Elevated IL-6 levels induce a burst of hypermetabolic activity leaning towards catabolism resulting from chondrocyte proliferation, and an elevated production of proteoglycans and collagens. IL-6 as well as other pro-inflammatory mediators induce significantly elevated levels of matrix metalloproteinases, as well as reactive oxygen species leading to cartilage extracellular matrix protein degradation and the loss of sulfated proteoglycans, collagens from the tissue [19].

This study has some limitations. First, the sample size was small (N= 100). Second, the levels of inflammatory biomarkers were measured in serum, as opposed to synovial fluid, which does not allow the detection of local autocrine or paracrine effects. Among the recruited patients, small number had an advanced K-L grade. This prevented a further exploring of the role of IL-6 in the late stage of KOA.

Further longitudinal trials are needed to better illustrate the association between SF inflammatory mediators and OA-related pain, knee function and radiographic severity.

5. Conclusions

Serum IL-6 level is high in primary KOA patients compared to healthy subjects, and is significantly linked to symptoms and radiographic severity. Targeting IL-6 signalling may be a novel and effective help for early detection of clinical evolution, improve symptoms and delay radiographic progression OA. The potential key role of IL-6 in the OA disease process and pathogenesis may lead to studies of IL-6 blockade as a therapeutic strategy in OA.

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Bashawyah, Martina Rekatsina, Yu-Ting Tai, Jui-An Lin, Giustino Varrassi: statistical analysis, co-writing, editing and revision of the manuscript. All authors have read and agreed to the published version of the manuscript.

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