The Egyptian Journal of Hospital Medicine (July 2023) Vol. 92, Page 6082- 6086

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

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ABSTRACT

Background: Osteoarthritis (OA) is the highest prevalent degenerative joint condition, leading to joint discomfort and impaired function.

Objective: This study aimed to examin the relationship among serum interleukin-6 (IL-6) and knee osteoarthritis (KOA) signs as well as the relationship among serum IL-6 and radiographic severity in cases with primary KOA.

Methods: This case-control research involved 50 primary KOA cases and 50 controls. Signs were measured through the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).

Results: Serum IL-6 was significantly elevated in OA cases than controls. WOMAC in OA cases ranged from 0 to 95 and Kellegren-Lawrence (KL) score mean was 2.7 ± 0.76. Serum IL-6 was significantly correlated with pain, physical function score, and radiographic score. Regression analysis revealed that IL-6 had a higher influence on WOMAC and KL score.

Conclusion: Serum IL-6 is elevated in KOA cases. In addition, serum IL-6 is associated with OA signs and radiographic severity.

Keywords: Primary knee osteoarthritis, Interleukin-6, WOMAC, Kellegren-Lawrence score, Visual analogue scale.

INTRODUCTION

Osteoarthritis (OA) is a gradual degenerative joint condition whose influence is growing as life expectancy increases [1].

OA impacts all joint tissues, leading to articular cartilage mass loss, subchondral bone remodeling, new bone production, and synovium inflammation [2]. Knee osteoarthritis (KOA) is considered the highest prevalent type of arthritis leading to pain and dysfunction, especially in elderly population [3].

Multiple causes are included in the OA development involving 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].

IL-6 is considered a pleiotropic cytokine which has 184 amino acid 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) acts as a significant supplier of IL-6 **[10].** Several research document the IL-6 catabolic impacts on cartilage and synovium with concomitant muscular degeneration, after traumatic events. High IL-6 serum level was identified as an independent prognostic factor of incident radiographic KOA [11].

The above-mentioned degenerative changes are related to pain and other OA signs that may result in limits in everyday activities, poor quality of life and functional impairment [12]. Therefore, more research into the commonest pathogenic factors can help to the development of novel treatment targets for OA [13]. This research objected to examine the possible relationship between serum IL-6 and KOA signs such as pain, stiffness and physical function as measured by WOMAC and to examine the connection among serum IL-6 and radiographic severity in primary KOA cases.

METHODS

This case-control research involved fifty patients who met the American college of rheumatology classification criteria for primary KOA [14] and a control group of fifty randomly chosen healthy individuals.

Exclusion criteria: (1) presence of any concomitant autoimmune, metabolic, infectious, or inflammatory disease; (2) secondary OA.

Ethical approval: This research was approved by the Local Research Ethical Committee of Tanta University (approval code 35105/12/21). Prior to inclusion, the participants gave an informed consents. The study meets the provisions of the Helsinki 1995 Declaration.

Received:12/2/2023
Accepted:12/4/2023

The data obtained were full medical history, body mass index (BMI), pain assessment by visual analogue scale (VAS), as well as laboratory investigations as serum IL-6. Serum IL-6 levels were immunoassayed by commercial ELISA kit provided 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).

The WOMAC [15] is a well validated self-reported outcome measure for KOA. It comprises 24 items classified into 3 subscales: pain (5 items), stiffness (2 items) and physical function (17 items), each one scored on a 5-point Likert scale (none, mild, moderate, severe, and extreme). Pain and physical function subscale scores ranged from 0 to 100 score (0 = no symptoms, 100 = extreme symptoms).

Standing anteroposterior knee radiographs were taken and assessed using the Kellegren-Lawrence (KL) grading tool [16]. KL grades were measured as: 0, 1, 2, 3 and 4, which represented as no OA radiographic features, possible joint space narrowing and osteophyte formation, definite osteophyte formation with possible joint space narrowing, multiple osteophytes, definite joint space narrowing, sclerosis, possible bony deformity, large osteophytes, marked joint space narrowing, severe sclerosis, and definite bone deformity respectively.

Statistical analysis

SPSS, version 20.0 was used. Data were presented as mean ± SD or median (IQR) for quantitative data and were compared by Student t-test or Mann Whitney test respectively and as number (%) for qualitative data and were compared by Chi-square test (Fisher or Monte Carlo). Spearman's correlation and logistic regression analysis were applied. $p \leq 0.05$ was considered significant.

RESULTS

There were no significant differences among cases and controls as regards sex, age, BMI, disease duration and family history (Table 1). The WOMAC score in OA cases ranged from 0 to 95 and in control group it was 0-1. The KL score mean was 2.7 ± 0.76 in the patients' group. There was a significant correlation among serum IL-6 and the VAS pain score, ESR levels, WOMAC score, and KL score (Table 2). Linear regression analysis demonstrated that serum IL-6 levels had the greatest influence on WOMAC and KL scores amongst those parameters (Table 3).

Table (1): Demographic features, scores, laboratory investigations and IL-6 in the studied groups

		Cases	Control	t. test	p. value
Sex	Male (%)	11 (22%)	16 (32%)	X^2: 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	15.791	**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	15.764	**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%	-		
IL – 6	Range	39 – 320	28 – 88	9.343	**0.001**
	Mean ± S.D	110.22 ± 46.98	46.04 ± 12.34		
Disease duration	Range	1 – 11	1 – 9	0.174	0.862
	Mean ± S.D	5.48 ± 2.57	5.40 ± 1.99		
Family history		40 (80%)	37 (74%)	X^2: 0.508	0.476
Chodroprtective		30 (60%)	18 (36%)	X^2: 5.769	**0.001**
NSAID		50 (100%)	50 (100%)	-	-

VAS: visual analogue scale, **BMI:** body mass index, **WOMAC:** Western Ontario and McMaster Universities Osteoarthritis Index, **IL-6:** interleukin 6. Bold values are significant as $P \leq 0.05$.

Table (2): Correlation between serum IL-6 with different parameters in primary KOA patients

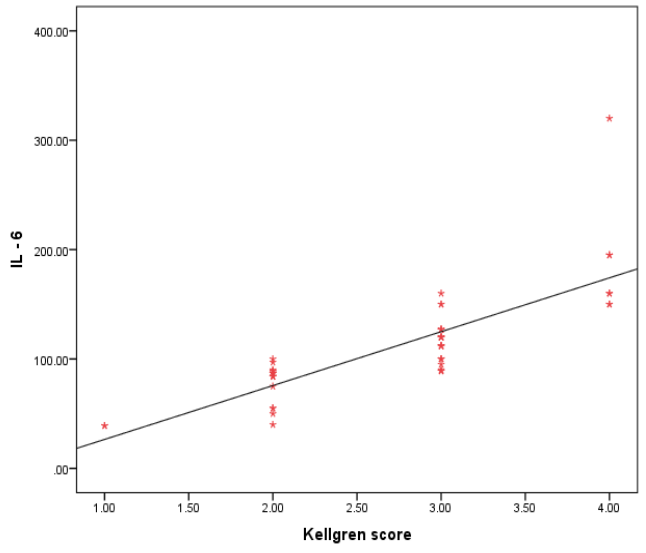
	IL – 6	
	r	**P value**
Age	-0.134	0.353
Disease duration	0.142	0.327
VAS	0.595	**0.001**
BMI	-0.017	0.904
WOMAC	0.666	**0.001**
ESR	0.548	**0.001**
CRP	0.109	0.452
KL score	0.799	**0.001**

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 as P ≤0.05.

Table (3): Linear regression analysis for parameters most influenced by serum IL-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 as P ≤ 0.05.



DISCUSSION

Serum and synovial fluid inflammatory mediators are believed to own a significant influence on cartilage metabolism and inflammation and may represent important pain therapy targets [2]. Higher production of IL-1, IL-6, and TNF- is related to pain in the early stages of knee osteoarthritis (KOA), suggesting that reducing inflammation may be more effective in relieving pain at this point [17]. As the synovial and subchondral inflammation importance in individuals with primary OA is increasingly acknowledged. This study examined the relationship among serum IL-6, KOA signs and radiographic severity. It showed that KOA cases had elevated 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]. Raised IL-6 in blood or synovial fluid correlates with disease incidence and severity in OA cases, although IL-6 has a crucial function in cartilage pathology, e.g. by inducing matrix-degrading enzymes [20]. In this research, serum IL-6 was also correlated with pain intensity measured by VAS score. Similarly, other authors reported significant relationships among IL-6 and knee pain [21, 22].

Pro-inflammatory cytokines play more than one function in the generation of pain in primary KOA. 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]. In addition to structural damage, pro-inflammatory cytokines can promote pain via peripheral and central sensitisation, mediated by C fibres [25] However, a recent research demonstrated that IL-6 was not found superior to placebo in hand OA cases, indicating that other factors might contribute to the complex phenomenon of OA [26]. Apart from synovitis, bone-marrow lesions, erosions, and bone attrition may contribute to nociceptive pain in hand OA [26].

Serum IL-6 was also correlated with the WOMAC. A former study demonstrated that IL-6 in the synovial fluid is significantly related to knee pain regarding the WOMAC [27]. Others have observed that there is no relationship among IL-6 and the WOMAC [28]. Inflammatory cytokines mediate pain at rest and with movement. Regarding OA, pain during motion is highly intense compared to at rest, correlates negatively with physical function, and manifests sooner in the disease course than pain at rest [29].

Multiple factors contribute to physical function impairment in OA patients. Low grade chronic inflammation leads to OA-related sarcopenia which impacts not just the neighbouring muscles of damaged joints, but all skeletal muscles as well [30, 31]. Individual variables linked with OA, as lack of physical activity and obesity, might indirectly contribute to the OA-related sarcopenia development [32]. Correspondingly, a reverse association has been reported among hamstring muscle resistance and serum IL-6 in OA older women, indicating that IL-6 has a significant function in OA sarcopenia [33].

In this research, elevated IL-6 was related to elevated KL grade and radiographic severity. Also, prior research demonstrated that people with a greater BMI and elevated IL-6 increased the likelihood of being diagnosed with verified radiographic KOA [34]. Also,

sex and genders are important on the late-stage KOA [35]. Other authors positively correlated synovial fluid and serum IL-6 with lesions intensity in x-ray imaging [22]. Elevated IL-6 levels induce a burst of hypermetabolic activity leaning towards catabolism due to chondrocyte proliferation, and an increased proteoglycans and collagens production. 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 sulfated proteoglycans and collagens loss from the tissue [19].

Limitations: First, there was a tiny sample size. Second, the inflammatory biomarkers were assessed in blood as opposed to synovial fluid that does not permit the identification of autocrine or paracrine effects at the local level. A tiny fraction of the enrolled patients had an advanced K-L grade. This hampered further investigations into the function of IL-6 in the advanced stage of KOA.

CONCLUSION

Serum IL-6 is raised in primary KOA cases compared to healthy subjects and is significantly linked to clinical signs and radiographic severity. Targeting IL-6 signaling may be a novel and effective help for early detection of clinical evolution, improve symptoms and delay radiographic progression OA. The putative critical IL-6 involvement in the disease process and OA pathogenesis might result in IL-6 blockage studies as a treatment option for OA.

- **Acknowledgments:** none.
- **Funding:** Nil.
- **Conflicts of interest:** Nil.

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