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Evaluation of Serum Interleukin-6 Level in grade II-III Knee Osteoarthritis: A Study of 61 Patients

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Abstract

Introduction: *Osteoarthritis (OA) is highly debilitating due to pain, stiffness, loss of function, disability and impaired quality of life. Currently, there is no effective treatment for OA because the pathophysiology of OA is poorly understood. To know whether inflammation is associated or not with OA, the aim of the present study was to assess serum interleukin-6 level in grade II-III knee OA.* ***Materials and Methods:*** *Adults with knee pain, radiologically diagnosed with mild to moderate (grade II-III) knee OA, participated in this observational, descriptive, cross-sectional study. X-ray of knee joint of total 61 patients were done and diagnosed as grade II or III knee OA by a competent physiatrist according to the Kellgren-Lawrence (K-L) radiographic grading scale in the department of physical medicine and rehabilitation at BMU from October 2023 to June 2024. Serum Interleukin-6 (IL-6) levels were measured by chemiluminescence immunoassay (CLIA) method at the Snibe Maglumi 2000+ system.* ***Results:*** *In this study, serum IL-6 level was found to be increased in 55 (90.16%) out of 61 patients. However, serum IL-6 level was found within normal range in rest of the 6 (9.84%) patients.* ***Conclusion:*** *Inflammation might be associated with the knee OA. Serum IL-6 level may be used as a biomarker to help the clinicians for diagnosis and target for the anti-inflammatory therapy of knee OA.*

Keywords: *Osteoarthritis, inflammation, interleukin-6.*

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Introduction:

Osteoarthritis (OA) is a serious, disabling condition[1]. In adults, OA is the most prevalent kind of arthritis[2]. OA affected 595 million of the global population in 2020[2]. Individuals with OA experience increased pain, stiffness, swelling, disability, exhaustion, depression, insomnia, limited activities, and loss of involvement in regular social, communal, and professional activities[3]. The economic cost connected with OA is enormous, spanning from direct treatment costs ($65.5 billion) to lost work productivity ($71.3 billion)[4]. For many years, it was assumed that OA was a non-inflammatory degenerative arthritis caused by wear and tear, however it is now believed that aberrant remodeling of joint structures is triggered by inflammatory mediators[5]. The pathological changes observed in OA joints include degeneration of the articular cartilage and ligaments, thickening of the subchondral bone, formation

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of osteophyte, variable degrees of synovial inflammation, and hypertrophy of the joint capsule[5]. Normally, AMPK enzyme is essential to maintain the metabolic homeostasis of bone. It has been found that abnormal AMPK activity was associated with synovial pathological changes in OA. Aging, low-grade inflammation, mechanical injury, and metabolic syndromes result in decreased AMPK activity. Impaired AMPK activity results in increased inflammation-mediated cartilage breakdown. Conversely, increased production of p-P65 and mTORC1 leads to NF-κ B, which in turn causes chondrocyte apoptosis, inflammation of the synovium, and aberrant subchondral bone remodeling[6,7]. Inflammation contributes significantly to the development of OA[8]. Synovitis occurs in around 50% of OA patients[9]. Synovitis is frequent in early and severe OA, and it has been connected with the development of cartilage degradation[10,11]. Interleukin-6 (IL-6) is an important pro-inflammatory mediator that plays both a diagnostic and prognostic function in OA[12]. The pooled estimate (mean) of IL-6 in blood of adult healthy individuals was 5.186 pg/ml (95% CI: 4.63-5.74 pg/ml) in a large meta-analysis[13]. Increased circulating IL-6 levels were strongly predictive of radiographic knee OA (RKOA) and cartilage degradation, as well as the prevalence and incidence of RKOA[14]. Serum IL-6 levels are also linked to synovial fluid levels and osteoarthritis pain[15]. IL-6 stimulates substance P's excitatory activity on dorsal root ganglion neurons, contributing to pain and hyperalgesia in inflamed tissues. Notably, IL-6-induced hyperalgesia is persistent and difficult to cure, suggesting a role in chronic pain[16,17]. IL-6 stimulates matrix mineralisation by producing basic calcium phosphate crystals, which causes proteoglycan loss. IL-6 may be directly involved in OA-related muscle degeneration[16,17.] Being recognized as a serious disease, no current therapies have been able to halt or delay OA progression satisfactorily[18]. Correct understanding of OA pathophysiology will enable the identification of a variety of potential therapeutic targets involved in the structural progression of OA[19]. To know whether inflammation is associated or not with OA, this cross-sectional study aimed to evaluate serum interleukin-6 level in grade II-III knee OA patients for the diagnosis and potential anti-inflammatory treatment option for OA.

Materials and Methods:

This study was an observational, descriptive, cross-sectional study conducted in the Department of Pharmacology, in collaboration with Department of physical medicine and rehabilitation and the Department of Laboratory Medicine of Bangladesh Medical University (BMU), Dhaka, Bangladesh. The research protocol was approved by the Institutional Review Board (IRB) of BMU after reviewing the scientific and ethical issues related to the research. The IRB of BMU issued a Clearance Letter (Memo No. BSMMU/2023/11020). Permission for the study was taken from the authority concerned. Convenient sampling was done. Total sample size was 61. The duration of the study was from October 2023 to June 2024.

Participants: The study was carried out among 61 patients with mild or moderate (grade-II or III) knee OA visiting the Outpatient Department (OPD) of the Department of Physical Medicine and Rehabilitation, BMU. Inclusion criteria were patients with knee pain and normal body weight for Asians (BMI: 18.5-22.9 kg/m^2) of both sex, age: 18-65 years old, and patients with radiological evidence of mild or moderate knee OA (grade II or III) in one or both knee joints according to the Kellgren-Lawrence (K-L) radiographic grading scale[20]. The exclusion criteria were patients with prior history of knee trauma or surgery, history of presence of systemic inflammatory conditions such as rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, gout or pseudogout, chronic diseases (including diabetes mellitus, cardiovascular, pulmonary, renal or hepatic impairment), those taking immunosuppressant, who had received an intra-articular steroid injection within 3 months of the study, pregnancy or lactation. All the patients attending the outpatient department of Physical Medicine and Rehabilitation, BMU, during the visit were given X-rays of the affected knee joints (anteroposterior and lateral views) in a standing position and were diagnosed as having mild or moderate (grade-II or III) knee OA according to the K-L radiographic scale by a competent physiatrist with a fellowship degree. Patients with major comorbidities or an inability to cooperate with study requirements were precluded from entry. There was no healthy patient as control in this study. The study objectives were explained to each participant. Before participating in the study, all subjects provided informed written consent. Participants' confidentiality was rigorously protected. No risk of physical or psychological harm was associated with the study. Procedure of Interleukin-6 measurement: With all aseptic precautions for venipuncture, 2 ml of blood was collected from all the participants from the Median Cubital Vein. Blood was then transferred to the Clot activator tube. The tubes were inverted gently several times for proper mixing of clot activator with blood and labelled for identification.

Blood tubes were kept upright for 60 minutes. Then centrifuged at 3500 rpm for 10 minutes. Then, the supernatant (serum) was collected to the Eppendorf tubes and labeled. Samples were preserved at -20°C and thawed before sample preparation for determination. Then, all the serum samples were sent to the Department of Laboratory Medicine, BMU for estimation of serum IL-6 level. Serum IL-6 levels were measured by chemiluminescence immunoassay (CLIA) method at the Snibe Maglumi 2000+ system.

Statistical analysis: Statistical analysis was done by Microsoft Office Excel 2016. Quantitative variables were presented as mean ± standard deviation (SD), while qualitative variables were represented as number and percentages (%). Appropriate analysis was done to fulfill

the objective of the study. Data is presented by tables based on the nature of data. A statistically significant p-value is < 0.05.

Results:

A total of 61 patients were enrolled based on the study's eligibility criteria. Baseline demographic and clinical characteristics of the participants like age, sex, BMI, family history, residence, smoking, disease duration, number of symptomatic knees and KL grading were assessed as postulated in Table-I . OA patients showed age variations ranging in between 23 years to 65 years. Mean age of the patients was 49.43 (±9.73) years. Patients from urban areas were affected by knee OA in 57.4% (35/61) of cases. 55.7% (34/61) of the knee OA patients were housewives. Positive family history and smoking habit were present only in 29.5% and 8.2% of patients respectively. 95.1% (58/61) of the study population had grade II knee OA. 70.5% (43/61) of patients had single knee OA (right>left) and 78.7% (48/61) had knee pain for up to 5 years.

Table-I: Demographic and clinical characteristics of participants at the time of enrollment (n=61)

Variables	Number (%)
Age	
20-30	2 (3.28 %)
31-40	11 (18.03 %)
41-50	24 (39.34 %)
51-60	15 (24.60 %)
>60	9 (14.75 %)
Sex	
Male	09 (14.7%)
Female	52 (85.3%)
Residence	
Urban	35 (57.4%)
Rural	26 (42.6)
Smoker	5 (8.2%)
Positive family history	18 (29.5)
Occupation	
Housewife	34 (55.7%)
Service/business	22 (36.1%)
Others	5 (8.2%)
Radiological Grading	
Grade II	58 (95.1%)
Grade III	3 (4.9%)
Affected Knee(s)	
Both	18 (29.5%)
Left	20 (32.8%)
Right	23 (37.7%)
Duration of Knee Pain	
≤5 year	48 (78.7%)
6 - 9 year	9 (14.7%)
≥10 year	4 (6.6%)

Interleukin-6 level

The lowest value for IL-6 in the blood of total 61 knee OA patients was 3.56 pg/ml. The highest among these values was 26.4 pg/ml. The mean ± SD of IL-6 among 61 patients was 10.71± 5.78 pg/ml.

Among the total 61 knee OA patients, serum IL-6 level was found to be increased in 90.16% (55/61) of the patients as shown in Table-II.

Table-II: Total distribution of IL-6 level (pg/ml) (n=61)

IL-6 level	Number (%)	Mean±SD	P value
Within normal value (≤5.74 pg/ml)	6 (9.84%)	4.66 ± 0.98	
Above normal value (>5.74 pg/ml)	55 (90.16%)	11.37± 5.70	0.006*
Total	61 (100%)	10.71± 5.78	

*; p<0.05; Unpaired t-test

was done between two groups.

39.34% (24/61) of the knee OA patients were found in the 5th decade and 24.60% (15/61) were in the 6th decade. Mean IL-6 level was highest (12.92 ±7.71pg/ml) in age group above 60 years as shown in Table-III.

Table-III: Age group distribution of IL-6 level (pg/ml) (n=61)

Age group (in years)	Number (%)	Mean±SD
20-30	2 (3.28 %)	5.72 ± 0.56
31-40	11 (18.03 %)	9.08 ± 4.18
41-50	24 (39.34 %)	10.20 ± 5.01
51-60	15 (24.60 %)	12.07 ± 6.64
>60	9 (14.75 %)	12.92 ± 7.71
	Total = 61 (100%)	

Among 55 patients with increased IL-6 levels, 85.3% (47/55) of the patients were female (male to female ratio 1:5.8). Mean IL-6 level in female knee OA patients was 11.47± 5.79 pg/ml where it was 10.78 ± 5.49 pg/ml in male OA patients as shown in Table-IV.

Table-IV: Sex wise distribution of increased IL-6 level (pg/ml) (n=55)

Male		Female		
Number (%)	Mean±SD	Number (%)	Mean±SD	P value
8 (13.11%)	10.78 ± 5.49	47 (77.05%)	11.47± 5.79	0.75[a]

aUnpaired t-test

In case of joint involvement, mean IL-6 level was 12.24± 6.92 pg/ml in patients with both knees OA where it was 11.01± 5.18 pg/ml in patients with single (right/left) knee OA as shown in Table-V. Mean IL-6 level in OA patients presenting with knee pain for more than 5 years was 11.45 ±4.72 pg/ml where it was 11.35 ± 5.94 pg/ml in OA patients presenting with knee pain for up to 5 years as shown in Table-V.

The difference in IL-6 levels between males and females, between single and both knees involvement, and between patients with knee pain for more than 5 years and those with knee pain for up to 5 years was not statistically significant.

Table-V: Distribution of increased IL-6 level (pg/ml) according to clinical symptoms (n=55)

Variables	Number (%)	Mean±SD	P value
Affected joint(s)			
Single knee OA[x]	39 (70.9%)	11.01± 5.18	0.47[a]
Both knee OA	16 (29.1%)	12.24± 6.92	
Duration of knee pain			
≤5 year	45 (81.82)	11.35 ± 5.94	0.96[a]
>5 year	10 (18.18%)	11.45 ±4.72	

x: either right/left knee; aUnpaired t-test

Discussion:

The present cross sectional study explored the serum concentration of proinflammatory cytokine IL-6 in patients with grade II-III knee OA and associated with clinical knee pain. It was found that all knee OA patients had 2-fold rise of serum IL-6 levels than normal value in healthy persons as suggested by meta-analysis. 90.16% knee OA patients had 2.5–fold increased serum IL-6 levels than normal IL-6 value which is comparable to previous studies[21,22]. Several authors identified the correlation of higher levels of serum IL-6 and knee OA as active OA patients had much greater amounts of IL-6 in their blood than healthy ones[21,23,24]. Interleukin-6 (IL-6), is a pleiotropic cytokine, that strongly stimulates the immune system and boosts the inflammatory response. IL-6 is produced by chondrocytes, osteoblasts, synovial fibroblasts or plasma cells, macrophages, and adipocytes in response to IL-1β and TNFα in joint tissues[25]. Distel et al. (2009) found that Infrapatellar Fat Pad from knee OA patients released significantly greater quantities of IL-6, but not TNF-α or IL-1β[26]. IL-6 signaling is a key player in OA pathogenesis. Classically, increased levels of IL-6 are related to development and progression of OA due to upregulation of metalloproteinase gene expression, stimulation of reactive oxygen species production, alteration of chondrocyte metabolism, and increased osteoclastic bone reabsorption[27,28]. We also found that most of the knee OA patients had grade-II knee OA (early stage of OA) and were within age group 40-60 years. IL-6 level was highest after 60 years of age which is similar to previous study[29].

The process called inflammaging indicates a regulation of the inflammatory response that occurs with aging can result in the production of inflammatory cytokines, which generates a low level of chronic proinflammatory condition 30. This may occur due to the presence of chronic diseases associated with aging such as OA, as well as other conditions such as obesity and physical inactivity[30].

We also found that mean IL-6 level was higher in female knee OA patients, patients with both knee OA and knee pain for >5 years than male OA patients, patients with single knee OA and knee pain for ≤5 years respectively.

A strength of the current study is that quantitative measurement of serum IL-6 was done by highly sensitive and specific chemiluminescence immunoassay (CLIA) method. CLIA is superior to ELISA as it has a greater detection range than ELISA[31]. Radiographic K-L grading was done by a competent physiatrist. There are limitations in our study. All the patients were not of same radiographic grade. Less than 5% patients had grade III OA as well. So, uniformity of the patients could not be ensured. There were no healthy controls in this study.

Conclusion:

Increased IL-6 level indicates inflammation in knee OA. Serum IL-6 level may be used as a biomarker to help the clinicians for diagnosis and target for the anti-inflammatory therapy of knee OA.

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Conflict of Interest: None.

Ethical approval: The protocol was approved by the IRB of Bangladesh Medical University (Memo no. BSMMU/2023/11020, dated 24 August 2023.

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