Original Article

Association of Interleukin-8 Levels with the Development of Uterine Leiomyomas

Masooma Talib,[1] Ayesha Javed,[2] Mariam Malik,[3] Muhammad Farhan Zafar,[4] Muhammad Shoaib[5]

Abstract

Objective: To find out the relationship between Uterine Leiomyoma and IL-8 levels.

Methodology: A cross sectional study was conducted on a sample of 100 females (age ranging from 25-50 years) including 50 ultrasound confirmed cases of uterine leiomyomas and 50 healthy controls for a duration of 6 months. Levels of plasma IL-8 were measured by ELISA technique.

Results: Irregular menstrual cycle was reported in about 44% of cases and 11% of controls. Mean number of fibroids in females was two. 54% of women were found to have small (<2cm) sized fibroids while 46% had large sized fibroids. Out of these 78% were intramural and 22% were sub-serosal type of fibroids. Plasma levels of IL-8 were positively correlated (p=0.001) with Uterine Leiomyomas.

Conclusion: IL-8 levels are significantly higher in patients with uterine leiomyomas depicting a positive correlation between IL-8 and the development of fibroids. However, further studies are required to better understand the role of IL-8 in the development of fibroids.

Keywords: Uterine Leiomyoma; IL-8, Risk Factors.

How to cite: *Talib M, Javed A, Malik M, Zafar MF, Shoaib M. Association of Interleukin-8 Levels with the Development of Uterine Leiomyomas. MedERA-Journal of CMH LMC and IOD.2023; 5(1): 19-22*

DOI: *doi.org/10.5281/zenodo.8307440*

Introduction

The most common benign tumor of smooth muscles in females of reproductive age is Uterine Leiomyoma (also known as fibroids) and it has significant negative impact on reproductive system. They can be single in number but are usually multiple and are associated with significant morbidity and deteriorating quality of life.[1,2] Leiomyomas are the cause of about 40-60% of total hysterectomies done worldwide.[3] Many predisposing factors for fibroids have been described and studied yet the exact pathogenesis is unknown. BMI, age, ethnicity and parity are associated with fibroids.[4]

Patients with uterine leiomyomas usually present with irregular menstrual cycles, dysmenorrhea, feeling of heaviness in the pelvis, pain, bleeding and anemia. Presentation of the patient varies with type, and location of the fibroids and likewise the treatment options are different for different types of fibroids. E.g., Sub-mucosal fibroids have a better response to GnRH as compared to the intra-mural types.[5] Severity of symptoms in patients with leiomyoma is associated with increasing size of the fibroids. Large fibroids usually degenerate over time because the blood supply becomes insufficient over time.[6]

1. *Watim Medical and Dental College, Rawalpindi*
2. *FMH College of Medicine and Dentistry, Lahore*
3. *Consultant Radiologist, THQ Pasrur*
4-5. *National University of Medical Sciences, Rawalpindi*

Correspondence:
Dr. Masooma Talib, *Associate Professor, Watim Medical and Dental College, Rawalpindi, Punjab, Pakistan. masooma.bilal@gmail.com*

Submission Date: 15-01-2023
1st Revision Date: 22-05-2023
Acceptance Date: 25-06-2023

Interlekin-8 (IL-8) is one of the major mediators of body's inflammatory response produced by macrophages and other cell types. Recent studies.[7,8] have associated the prevalence of fibroids to a higher circulating level of circulating IL-8. Recently increase in circulating levels of IL-8 has been associated with the prevalence of leiomyomas. IL-8 is a chemokine produced by macrophages and other cell types. It is one of the major mediators of inflammatory response. Studies[7,8] indicate an increased expression of IL-8 on the uterine leiomyomas. IL-8 and IL-9 receptors are associated in the pathogenesis of this disease. A better understanding of role of IL-8 in the hormone-driven growth of fibroids is critical in the development of target-selective therapies for this rampant condition. Our study is focused to explore the association of IL-8 with the prevalence of fibroids.

Methodology

Ethical Ref No: UHS/Education/126-13/1523. This was a cross-sectional study spanning over a period of 6 months at Lahore General Hospital after taking permission from Institutional Review Board. 100 women were included in the study with non-convenient probability sampling. 50 women with fibroids confirmed by ultrasound were included as 'cases' and 50 healthy women were taken as 'control'. Women with pregnancy or other conditions associated with raised IL-8 levels were excluded.

A written informed consent was taken from the patients before the study. The fibroid diameter in 'cases' was measured using ultrasound and categorized as small (<2 cm size) and large (≥2 cm).

A venous blood sample was collected from each patient (5ml each in EDTA tubes). It was centrifuged and serum was isolated and stored at -20°C. Plasma levels of IL-8 were measured using Enzyme Linked Immunosorbent Assay (ELISA) technique. The reference range used for IL-8 is 3.202+1.33pg/ml.

The data collected from the 'cases' and the 'controls' were stored, analyzed, and tabulated using SPSS version 25. Independent t test was used as a test of significance and a p-value of <0.05 was considered statistically significant.

Results

Table 1 shows the pattern of menstrual cycle in cases and controls separately. It describes the frequency of irregular cycles noted in both the groups. Table 2 describes the number, type, and size of fibroids in frequency and percentages. The most common type observed was 'Intramural' (78%). The mean IL-8 levels in the cases were 13.198 + 5.851 pg/ml and in the controls were 3.202 + 1.333 pg/ml. A statistically significant difference is present between the two groups (p = 0.001).

Table 1: *Distribution of cases and control by age and menstrual regularity*

Characteristic	Cases (n=100)	Controls (n=100)	P value
Age (years)	34.74±6.5	36.36±7.86	0.063
Menstrual regularity:			
Regular	28(56%)	41(82%)	0.001*
Irregular	22(44%)	9(18%)	0.015*

*p value significant at <0.05

Table 2: *Distribution of characteristics of fibroids in all cases*

Fibroid characteristics	Frequency (n=100) (percentage %)
Number of fibroids	
i. One	19 (38%)
ii. Two	15 (30%)
iii. Three	16 (32%)
Size of fibroid	
i. Small	27 (54%)
ii. Large	23 (46%)
Type of fibroid	
i. Intramural	39 (78%)
ii. Subserosal	11 (22 %)

Table 3: *Comparison of IL-8 levels amongst cases and controls*

Variable	Cases (n=100)	Controls (n=100)	P value
Interleukin 8 (pg/ml)	13.19 + 5.85	3.2 + 1.33	0.001*

*p value significant at <0.05

Discussion

The current study was carried out among 50 cases and 50 controls to compare the circulating levels of IL-8 between the two groups. Mean age of the 'cases' was 34.74+6.50, and that of controls was 36.36+ 7.86. 74% of cases and 66% of controls had the age ranging 35-50 which is consistent with the observations of previous studies[9,10] that uterine leiomyomas are prevalent in the 3rd and 4th decade of life.[9,10]

In our study, menstrual irregularity was noted in 44% of patients and 18% of controls but the difference was not statistically significant. The reason might be in the fact that 9-14% of otherwise healthy women also report to have menstrual irregularities while it is quite common in multiparous women.

The mean IL-8 levels in the cases were 13.198 + 5.851 pg/ml and in the controls were 3.202 + 1.333 pg/ml. This shows a significantly higher value in patients with fibroids as compared to the healthy females. This result was statistically significant (p=0.001) and reflects that high levels of IL-8 are associated with the presence of fibroids. Other studies[11,12] have demonstrated an increased expression of IL-8a receptors and elevated levels of circulating IL-8 in patients with uterine leiomyomas as well, and this association has been implicated further in a study[12] demonstrating the inhibition of myometrial proliferation with blockade of IL-8a receptors with the help of neutralizing antibodies. Our study also backs this association of IL-8 with Uterine Leiomyomas.

By studying the role of inflammatory markers like IL-8, the cellular mechanisms responsible in the pathogenesis of fibroids can be further identified clearly. This will help in the development of targeted therapies directed against the diseases.

Conclusion

IL-8 levels are significantly higher in patients with uterine leiomyomas depicting a positive correlation between IL-8 and the development of fibroids. However, further studies are required to better understand the role of IL-8 in the development of fibroids.

Conflict of Interest *None*

Funding disclosure *None*

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Authors Contribution

MT: Conceptualization of study, Writing of Manuscript
MM: Literature Search
MFZ: Statistical Analysis
AJ: Data Collection and Analysis
MS: Drafting, Revision
MT: Writing of Manuscript

All authors are equally accountable for accuracy, integrity of all aspects of the research work.