Uterine Leiomyoma in Relation to Insulin like Growth Factor-1

MASOOMA TALIB¹, AAMENAH MALIK², NADIA MAHMOOD³, MARYAM MALIK⁴

ABSTRACT

Background: Uterine leiomyoma is a very common benign smooth muscle tumor of the uterus. It is the most frequent benign neoplasm in women of reproductive age and could have a harmful impact on the reproductive system. Insulin-like growth factor–I (IGF-I) plays a vital role in the pathogenesis of fibroids.

Aim: To find out the relationship of uterine leiomyoma with insulin like growth factor -1.

Study design: Cross sectional study

Methods: A Cross Sectional study for duration of 6 months (May 2013- Nov 2013) was designed. 50 women with uterine fibroids (confirmed by USG) with age range of 25-50 years with confirmed report of fibroid USG, were included in the study. A group of 50 women with no history of disease were taken as controls. Level of plasma IGF-1 was measured by ELISA.

Results: About 44% cases and 11% controls had irregular menstrual cycle. An average of two fibroids was noted. About 54% women have small size fibroid (<2cm) and 46% have large size fibroid. Intramural fibroid was observed in 78% and subserosal in 22%. Level of plasma IGF-1 was significantly increased in patients as compared to controls.

Conclusion: It is concluded that there is a direct relationship of uterine leiomyomata with IGF-1. However, more research is needed to find out the association of IGF-1 with the onset of myoma and its growth.

Keywords: Leiomyoma, IGF-1, risk factors.

INTRODUCTION

Uterine leiomyomas are the most frequent benign neoplasm in women of reproductive age and can have a harmful impact on the reproductive system. Their number may be single but in most cases these are multiple, causing morbidity, and worsening of quality of life. About 40-60% of hysterectomies are done due to myomas.

Though the exact etiology of fibroids is not known, many predisposing factors have been associated with fibroid. These include age, ethnicity, weight and nulliparity. The most common presentation of fibroid patients include menstrual irregularities, anemia, dysmenorrhea and pelvic pain and pressure. In clinical practice, the location of fibroid is important because they partially differ in symptoms and surgical treatment. Intramural fibroids tend to bleed more owing to their location. Sub mucosal fibroids generally show a stronger response to GnRH treatment and can often be surgically removed in contrast to intramural fibroids. Symptomatic patients usually reveal larger fibroids on ultrasound. Large fibroids often degenerate when their blood supply becomes insufficient gradually.

Insulin-like growth factor–I (IGF-I) plays a vital role in the pathogenesis of fibroids. It is raised in about one third of patients with fibroids. IGF-I stimulates the mitosis of fibroid cell and a significantly increased levels were observed in large size fibroids as compared to small ones. Increased expression of IGF-I, up regulation of gene expression and protein in fibroid is reported by a number of studies. Estrogen-dependent IGF-I up regulation and its relationship to transcription factors may increase anti-apoptotic and proliferative effects in the tissue of uterine leiomyoma.

Hence, a complex interplay between the receptor of IGF-1, other growth factors and hormonal factors may be responsible for the development of leiomyoma. So our study set out to explore further the role of IGF-1 in the pathogenesis of uterine leiomyoma.

MATERIAL AND METHODS

A Cross sectional study for duration of 6 months (May 2013- Nov 2013) was designed. 50 women age range 25-50 year with uterine fibroids (confirmed by USG) were taken from Lahore General Hospital. Women with pregnancy or any other disease which was associated with disturbed IGF-1 levels were excluded from the study. The fibroid diameter was categorized as the tumor diameter, as a continuous variable (small; <2cm and large; ≥2 cm).
A group of 50 women with no history of any disease were taken as controls. Prior consent of all subjects was taken. About 5 ml venous blood was collected in blood collection tubes containing EDTA. Serum was separated and stored at -20°C. Levels of plasma IGF-1 was measured by ELISA ((Elecsys 2010, Roche Diagnostics, Germany). Reference range of IGF-1 = 22 - 197 ng/ml.

**Statistical analysis**: The data was analyzed using SPSS 20. Independent t test was used to compare the levels of different variables amongst groups. P-value of <0.05 was considered statistically significant.

Table 1: Distribution of cases and controls by menstrual regularity.

<table>
<thead>
<tr>
<th>Menstrual regularity</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular</td>
<td>28(56%)</td>
<td>41(82%)</td>
</tr>
<tr>
<td>Irregular</td>
<td>22(44%)</td>
<td>9(18%)</td>
</tr>
<tr>
<td>Total</td>
<td>15(100%)</td>
<td>15(100%)</td>
</tr>
</tbody>
</table>

P value: 0.015(<0.05)**

Table 2: Characteristics of fibroids in cases.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of fibroid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>One</td>
<td>19</td>
<td>38</td>
</tr>
<tr>
<td>Two</td>
<td>15</td>
<td>30</td>
</tr>
<tr>
<td>Three</td>
<td>16</td>
<td>32</td>
</tr>
<tr>
<td>Size of fibroids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small</td>
<td>27</td>
<td>54</td>
</tr>
<tr>
<td>Large</td>
<td>23</td>
<td>46</td>
</tr>
<tr>
<td>Type of fibroid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intramural</td>
<td>39</td>
<td>78</td>
</tr>
<tr>
<td>Subserosal</td>
<td>11</td>
<td>22</td>
</tr>
</tbody>
</table>

**RESULTS**

Table 1 represents the menstrual pattern of cases and controls. Our cases had a significantly higher frequency of irregular menses. About 44% of cases and 18% of controls had irregular menstrual cycle (p value 0.015) Characteristics of fibroids are given in table 2. It is observed that 38% of women have only one fibroid, 32% have three fibroid and 30% have two fibroid. About 54% women have small size fibroid and 46% have large size fibroid. Intramural fibroid was observed in 78% and subserosal in 22%. Variation in the level of IGF-1 in women with uterine leiomyoma is given in figure 1. Level of plasma IGF-1 was significantly increased in patients as compared to control subjects (88 versus 213 ng/ml) and it showed a highly significant difference (P<0.001)

**DISCUSSION**

Uterine fibroids are one of the most common pelvic pathology in females, occurring in almost 20 – 40% females during their reproductive age. Leiomyomas have been depicted as hormonal and clonally regulated, but etiology and mechanism involved in the growth remains unknown. To date, a lot many factors have been labeled that affect the endometrium of the normal uterine tissue to develop into a fibroid. Amongst these factors, IGF-1 plays a significant role in development of leiomyoma. In vitro studies have shown that uterine fibroid cells proliferate in the presence of IGF-1 by stimulating signaling pathways.

The present study was done among 50 cases (females with fibroid uterus) and 50 controls to compare the mean values of IGF-1 in the two groups. In our study, menstrual irregularity was observed in 44% cases, while only 18% controls had menstrual irregularities. The difference between the two groups was significant and has been proven before in a number of studies. Since, menstrual irregularities are seen in 9–14% of population of healthy women. It was noted in this study that women who were diagnosed with fibroids not only had menstrual complaints but also lower abdominal swelling which was misinterpreted as weight gain after child birth.

In this study, 38% patients had a single fibroid. This frequency is lower than that observed by Oliveira et al, with 62% patients had a single fibroid. The possible explanation for this difference was that this study was conducted in Europe. Europeans being more educated and concerned about the health status, contact at earlier stage of the disease. On average, women had 2 fibroids which are consistent to a study which found similar results. Another study suggested that fibroids present on the outer side of myometrium are less likely to take part in abnormal uterine bleeding. In the present study, majority i.e., 78% cases had intramural fibroids and 22% cases had subserosal fibroid. This higher proportion of intramural fibroids was also confirmed by Oliveira et al. Another study by Brolmann et al. had a similar observation. The difference in frequency of small and large size fibroids was not

**Fig. 1: Comparison of IGF-1 levels in cases and controls**
significant with 54% had small size fibroids and 46% had large fibroids. However in study by Oliveira et al, 60% of the patients had large sized fibroids.

We compared the mean (SD) level of IGF-1 in both cases and controls. A higher mean value of IGF-1 was found in cases (213.18±64.74 ng/l) as compared to controls (88.52±29.77ng/l). The difference between the two groups was significant. In a study by Tang, et al, this had been proven that human uterine tissues contain IGF-I. IGF-I is found to be a powerful mitogenic agent in human endometrial stromal and myometrial smooth muscle cells, and its maximum effect on DNA synthesis is seen at a level of 100ng/ml. It leads to an increase in proliferation of leiomyoma by activating MAP-Kinase pathway. It plays crucial role in leiomyoma cell growth by up-regulating Bcl-2 protein expression in leiomyoma cells. A study by L Levy found an association of bio-regulatory system of IGF-I with the growth and occurrence of leiomyoma.

CONCLUSION

It is concluded that significantly raised IGF-1 levels were seen in patients of uterine leiomyoma. However, more research is needed to find out the interplay of IGF-1 with other known factors in development of uterine leiomyoma.

REFERENCES
