

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^{1,2}. About 40-60% of hysterectomies are done due to myomas³.

Though the exact etiology of fibroids is not known, many predisposing factors have been associated with fibroid. These include age, ethnicity, weight and nulliparity⁴. 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 fibroids⁵. Symptomatic patients usually reveal larger fibroids on ultrasound. Large fibroids often degenerate when their blood supply becomes insufficient gradually⁶.

Insulin-like growth factor-I (IGF-I) plays a vital role in the pathogenesis of fibroids⁷. 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 ones⁸. Increased expression of IGF-I, up regulation of gene expression and protein in fibroid is reported by a number of studies^{9, 10}. 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^{11,12,13,14}.

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).

¹Asst Prof. Biochemistry, Yusra Medical College, Islamabad.

²Assistant Professor Biochemistry, C.M.H. L.M.C., Lahore.

³Associate Professor, C.M.H. L.M.C., Lahore.

⁴S R Radiology, Services Institute of Medical Sciences, Lahore

Correspondence to Dr. Nadia Mahmood Email: nadia_ather@hotmail.com Cell: 03004325114

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 ((Elecys 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

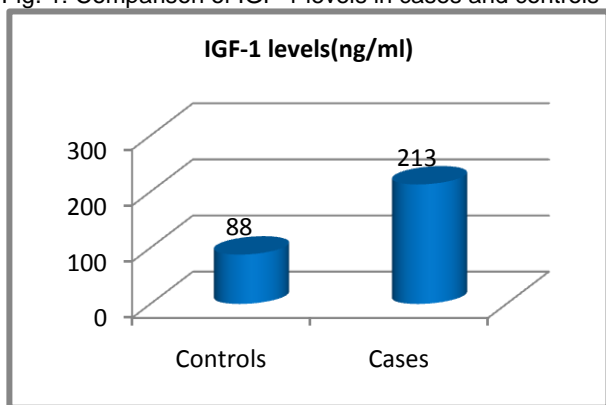
Menstrual regularity	Cases	Controls
Regular	28(56%)	41(82%)
Irregular	22(44%)	9(18%)
Total	15(100%)	15(100%)

P value: 0.015(<0.05)**

Table 2: Characteristics of fibroids in cases.

Variables	Frequency	%age
Number of fibroid		
One	19	38
Two	15	30
Three	16	32
Size of fibroids		
Small	27	54
Large	23	46
Type of fibroid		
Intramural	39	78
Subserosal	11	22

Fig. 1: Comparison of IGF-1 levels in cases and controls



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 unknown¹⁵. 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 pathways¹⁶.

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^{17,18,19,20}. 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 results²¹. Another study suggested that fibroids present on the outer side of myometrium are less likely to take part in abnormal uterine bleeding²². 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^{23,24}. The difference in frequency of small and large size fibroids was not

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 fibroids²⁴.

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/ml²⁵. It leads to an increase in proliferation of leiomyoma by activating MAP-Kinase path²⁶. It plays crucial role in leiomyoma cell growth by up-regulating Bcl-2 protein expression in leiomyoma cells²⁷. A study by L Levy found an association of bio-regulatory system of IGF-I with the growth and occurrence of leiomyoma²⁸.

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

- Sparic R, Mirkovic L, Malvasi A, Tinelli A/ Epidemiology of Uterine Myomas: Review. *Int J Fertil Steril*. 2016 Jan-Mar; 9(4): 424–435.
- Downes E, Sikirica V, Gilabert-Estelles J, et al. The burden of uterine fibroids in five European countries. *Eur J Obstet Gynecol Reprod Biol*. 2010; 152(1):96–102.
- Sparic R, Hudelist G, Berisavac M, Gudovic A, Buzadzic S. Hysterectomy throughout history. *Acta Chir Iugosl*. 2011; 58(4): 9–14
- Fleischer R, Weston GC, Vollenhoven BJ, Rogers PA. Pathophysiology of fibroid disease: angiogenesis and regulation of smooth muscle proliferation. *Best Pract Res Clin Obstet Gynaecol*. 2008; 22(4):603–614.
- Ivo Brosens, Jan Deprest, Paola Dal Cin, Herman Van den Berghe. Clinical Significance of Cytogenetic Abnormalities in Uterine Myomas. *Fertility and Sterility*, 98; 69: 232-5
- Roy, C., Bierry, G., El-Ghali, S., Buy, X. Acute torsion of uterine leiomyoma: CT features. *Abdom. Imaging* 2005; 30:120-3.
- Vollenhoven BJ, Herington AC, Healy DL. Messenger ribonucleic acid expression of the insulin-like growth factors and their binding proteins in uterine fibroids and myometrium. *J Clin Endocrinol Metab*. 1993;76:1106–1110.
- Baird DD, Travlos G, Wilson R, Dunson DB, Hill MC, et al. Uterine leiomyomata in relation to insulin-like growth factor-I, insulin and diabetes. *Epidemiology*. 2009;20(4):604–610
- L Peng, Y Wen, Y Han, A Wei, G Shi, M Mizuguch. Expression of insulin-like growth factors (IGFs) and IGF signaling: molecular complexity in uterine leiomyomas *Fertil Steril*. 2009 Jun;91(6):2664-75
- R Druckmanna, U.D Rohrb. IGF-1 in Gynaecology and Obstetrics: Update. *Maturitas*. 2002;41: 65–83
- Swartz CD, Afshari CA, Yu L, Hall KE, Dixon D. Estrogen-induced changes in IGF-I, Myb family and MAP kinase pathway genes in human uterine leiomyoma and normal uterine smooth muscle cell lines. *Mol Hum Reprod* 2005;11:441–50
- T Maruo, N Ohara, J Wang, H Matsuo. Sex steroidal regulation of uterine leiomyoma growth and apoptosis Human reproduction update. 2004;10(3):207-220.
- Radin RG1, Palmer JR, Rosenberg L, Kumanyika SK, Wise LA. Dietary glycemic index and load in relation to risk of uterine leiomyomata in the Black Women's Health Study. *Am J Clin Nutr*. 2010 May;91(5):1281-8.
- Wolanska M, Bankowski E. An accumulation of insulin-like growth factor I (IGF-I) in human myometrium and uterine leiomyomas in various stages of tumour growth. *Eur Cytokine Netw* 2004;15:359–63
- Aaron K. Styer, Jose M. Teixeira, Arno E. Commandeur1, Epidemiological and genetic clues for molecular mechanisms involved in uterine leiomyoma development and growth. *Hum. Reprod. Update* 2015, doi:10.1093/humupd/dmv030.
- Gkioka E1, Msaouel P2, Philippou A1, Vlahogiannis N1, Vogkou CT1, Margiolis A3, Koutsilieris M4. Review: The Role of Insulin-like Growth Factor-1 Signaling Pathways in Uterine Leiomyoma. *In Vivo*. 2015 Nov-Dec;29(6):637-49.
- Terry KL, De Vivo I, Hankinson SE, Missmer SA. Reproductive characteristics and risk of uterine leiomyomata. *Fertil Steril*. 2010;94(7):2703–2707.
- Wise LA, Palmer JR, Harlow BL, et al. Risk of uterine leiomyomata in relation to tobacco, alcohol and caffeine consumption in the Black Women's Health Study. *Hum Reprod* 2004;19:1746–54
- Terry KL, Missmer SA, Hankinson SE, Willett WC. Lycopene and other carotenoid intake in relation to risk of uterine leiomyoma. *Am J Obstet Gynecol*. 2008;198(1):37, e1-e8.
- Mauskopf J, Flynn M, Thieda P, et al. The economic impact of uterine fibroids in the United States: a summary of published estimates. *J Womens Health Larchmt* 2005;14:692–703.
- D. Selo-Ojeme, O. Lawal, J. Shah, R. Mandal, S. Pathak. The incidence of uterine leiomyoma and other pelvic ultrasonographic findings in 2,034 consecutive women in a north London hospital| Published online: 02 Jul 2009 ;421-3. <http://dx.doi.org/10.1080/01443610802149863>
- Laughlin-Tommaso SK1, Borah BJ2, Stewart EA3. Effect of menses on standardized assessment of sexual dysfunction among women with uterine fibroids: a cohort study. *Fertil Steril*. 2015 Aug;104(2):435-9.
- Brolmann H, Bongers M, Garza-Leal JG, Gupta J, Veersema S, Quartero R, Toub D. The FAST-EU trial: 12-month clinical outcomes of women after intrauterine sonography-guided transcervical radiofrequency ablation of uterine fibroids. *Gynecol Surg*. 2016; 13: 27–35.
- Oliveira, F.G., Abdelmassih, V.G., Diamond, et al. Impact of subserosal and intramural uterine fibroids that do not distort the endometrial cavity on the outcome of in vitro fertilization–intracytoplasmic sperm injection. *Fertil Steril*. 2004;81:582.
- Zhao Y, Zhang W, Wang S. The expression of estrogen receptor isoforms alpha, beta and insulin-like growth factor-I in uterine leiomyoma. *Gynecol Endocrinol* 2008;24:549–54
- Qiang Zhang, Shu-Hui Liu, Mark Erikson, Martyn Lewis, Dr. Elaine Unemori Relaxin activates the MAP kinase pathway in human endometrial stromal cells. *Journal of Cellular Biochemistry* 2002; 85: 536–44.
- Zhijian Gao, Hiroya Matsuo, Yin Wang, Satoshi Nakago, and Takeshi Maruo, Up-Regulation by IGF-I of Proliferating Cell Nuclear Antigen and Bcl-2 Protein Expression in Human Uterine Leiomyoma Cells. *Online*. April 26, 2011. <http://dx.doi.org/10.1210/jcem.86.11.8008>.
- Levy BS. Modern management of uterine fibroids. *Acta Obstet Gynecol Scand*. 2008;87(8): 812–823.

