Zagazig University Medical Journal
www.zumj.journals.ekb.eg
https://doi.org/10.21608/zumj.2023.235465.2882 Volume 31, Issue 1.1, JAN. 2025, Supplement Issue
Manuscript ID ZUMJ-2309-2882
DOI 10.21608/zumj.2023.235465.2882
ORIGINAL ARTICLE

Vascular Endothelial Growth Factor and Interleukin 1-b Gene Polymorphisms as a Genetic Predictor for Uterine Leiomyoma

Marwa Kamal Mohamed Abdelghany *[1], Haidy Zidan [2], Hala Elsayed Mohamed Mowafy [3], Shereen Mohamed ElShabrawy [2]
[1] Medical Biochemistry Department, Faculty of Medicine, Helwan University
[2] Medical Biochemistry, Faculty of Medicine, Zagazig University
[3] Obstetrics and Gynecology Department, Faculty of Medicine, Zagazig University

Corresponding author
Marwa Kamal Mohamed Abdelghany

Email:
Marwaelfeky.me@gmail.com

Submit Date 10-09-2023
Revise Date 11-09-2023
Accept Date 13-09-2023

ABSTRACT

Background: The most frequent benign gynecological tumor in premenopausal women is leiomyoma, generally known as fibroids. Leiomyomas have a significant financial effect, impacting an estimated 11 million women. This study aimed to better understand the genetic causes of uterine leiomyoma and predict the role of the polymorphism VEGF and IL1-b genes and uterine leiomyoma (UL) occurrence. **Methods:** This comparative study was conducted on 102 cases divided into two groups; 51 UL patients with matched age and sex and 51 healthy females of reproductive age as a control group. Genotyping of VEGF 460 and IL1b (-511) single nucleotide gene polymorphism by T-ARMS PCR. **Results:** The VEGF-460 (TT) Gene Polymorphism was significantly dominant (15.2 fold) in the UL group as compared with the healthy participants (p=0.0001). The IL-1b (CC) Gene Polymorphism was significantly dominant by (5 fold) in the uterine leiomyoma group as compared with the healthy control (p=0.0001). The combined "TT" VEGF-460 Gene Polymorphism and "CC" IL-1b polymorphism at position +511 was significantly dominant by (10.3 fold) in the UL group as compared with the healthy cases (p=0.0001). **Conclusions:** Patients with uterine leiomyoma were associated with a marked increase in VEGF-460 (TT) and IL-1b polymorphism Gene Polymorphism compared to leiomyoma-free ones. Such outcomes were proved in all gene and allele frequencies. However, combined "TT" VEGF-460 Gene Polymorphism and "CC" IL-1b polymorphism at position +511 was significantly dominant in the UL group as compared with the healthy control group.

Keywords: Vascular Endothelial Growth Factor, Interleukin 1-b, Gene Polymorphisms, Uterine Leiomyoma.

INTRODUCTION

Uterine leiomyomas (ULs) are among the most prevalent benign gynecological tumors that cause substantial mortality in women and are associated with a variety of problems. Local mass impact, pressure on nearby organs, heavy uterine bleeding, anemia, pregnancy-related problems, and infertility are the most common consequences [1]. Treatment of markedly complicated cases may necessitate invasive procedures such as hysterectomy [2].

Worldwide, the incidence of Uterine leiomyomas is about 60% in women under the age of 45 and this incidence has risen to 80 % of women aged of 50s, at least 30% of the cases are symptomatic. Uterine leiomyoma prevalence in Middle Eastern women was 30.6% [3].

Many previous studies tried to explain the pathogenesis of uterine leiomyoma, yet the exact pathogenesis is still obscure [4].

Risk factors for the development of uterine leiomyomas include both controllable and non-modifiable factors. Age, race, genetic pattern, environmental and lifestyle factors (diet, alcohol and caffeine intake, smoking, stress, and physical activity), steroid hormones (endogenous and exogenous), and growth factors all play a part in the genesis and growth of uterine fibroids. The immune system's role is among the highlighted pathogenesis in this disease [5].

Several studies have revealed that leiomyoma has a hereditary predisposition. Familial aggregation also suggests that genetic factors play a key part in the disease's origin. These facts are favored by a Korean study that was conducted in 2017. This study claimed clear racial disparity in African women with an obvious increase in the development and severity of the disease [6]. Identifying the genes implicated in leiomyoma could lead to new types of medication and possibly even prevention of this disorder [7].

Growth factors are involved in the pathogenesis of leiomyomas as they regulate angiogenesis, and they are important in fibrotic processes [8]. Vascular endothelial growth factor (VEGF) is an important growth factor family member. VEGF is a potent proangiogenic factor. Many previous studies used VEGF as a prognostic marker for a disease whose pathogenesis includes angiogenesis such as diabetic angiopathies and many types of tumors [9].

VEGF has an immunoreactivity effect on tumor cells and stromal matrix. This may contribute to tumor cell growth in a paracrine manner through angiogenesis and increased vascular permeability. Continuous exposure to VEGF may potentially increase the effect of other risk factors such as sex hormones that increase the vascular supply of the ovary and enhance the development of leiomyomas [10].

According to the previously discussed risk factors, the immune system's role is among the highlighted pathogenesis in this disease. Linking immunity, inflammation, and uterine leiomyoma may greatly help in disclosing the obscure pathogenesis. A few previous studies linked the Polymorphism in the Interleukin - 1b (IL-1b) gene with UL development [11].

IL-1b is a cytokine that belongs to the IL family and is engaged in immunomodulatory and inflammatory events throughout tumor formation in leiomyoma and other diseases such as gastric cancer. It is mainly generated by monocytes and macrophages during both inflammatory phases and has been linked to the pathophysiology of several inflammatory disorders, including atherosclerosis, bowel disease, peritonitis, and rheumatoid arthritis [12].

Polymorphisms in (IL-1b) and (VEGF) increase the susceptibility and the occurrence of many neoplasms and immunity diseases [13].

Since polymorphism in these genes is related to numerous immunomodulatory and inflammatory processes, we hypothesized that polymorphisms in promotor areas in these mediators that are known to be linked with increased expression might be associated with leiomyoma incidence.

The present study aims to give a better understanding of the genetic causes of uterine leiomyoma and predict the role of the polymorphism VEGF and IL1-b genes and uterine leiomyoma occurrence.

METHODS

Patients:

This study was carried out at the Medical Biochemistry& Molecular Biology and Obstetrics and Gynaecology Departments, Faculty of Medicine, Zagazig University. This study is a case-control study, including (102) subjects who were categorized into two groups: **Group (1):** includes 51 healthy females in reproductive age as a control group. **Group (2):** includes 51 uterine leiomyoma patients. The study was agreed upon by the research ethics team of the Faculty of Medicine, University of Zagazig. Written informed consent was obtained from all participants.

The research was conducted following the World Medical Association's Code of Ethics (Helsinki Declaration) for human research. The Institutional Review Board has given approval for this research (#10003/25-10-2022).

Inclusion criteria: Cases with the following criteria were included; Age between 30 and 45-year-old female, BMI ranging between 25-35, and cases diagnosed with uterine leiomyoma.

Exclusion criteria: Cases with the following characteristics were excluded; any other gynecological disease (adenomyosis, endometrial hyperplasia, cancer, etc.), any medical disorder (hypertension, diabetes, etc.), and previous history of pre-eclampsia.

Methods:

A complete assessment was done for each participant including Full history taking, complete physical and clinical examination, and routine investigations (transvaginal sonography and fasting blood sugar). Other investigations were done for selected cases (sonohysterography, hysteroscopy, magnetic resonance imaging to suspicious cases).

Plasma glucose level:

The plasma sample containing glucose was treated with (glucose oxidase-peroxidase reagent) containing hydroxy benzoate-4-amino antipyrine. The intensity of color was directly proportional to the concentration of D-glucose in the sample. The estimation was done by enzymatic colorimetric method using Spinreact kit, Girona, Spain. The measuring process according to Simonis-Bik et al. [14].

DNA extraction:

The DNA Extraction Kit (Beijing Solarbio Science & Technology Co., Lt) was used to extract genomic DNA from whole blood.

20 µl of each extracted DNA sample was combined with 1 ml of deionized water in a quartz cuvette to assess the concentration and purity of the DNA. The Milton Roy Spectronic 3000 Array was then used to detect the absorbance at 260 and 280 nm. Pure double-stranded DNA has an A260/A280 ratio that ranges from 1.7 to 1.9.

Genotyping of VEGF_460 single nucleotide gene polymorphism by Tetra-primer amplification refractory mutation system PCR (T-ARMS PCR):

All of the reagents were analytical PCR materials that had been thoroughly purified. To avoid contamination, all of the tubes, tips, and pipettes used for DNA extraction were DNAse and RNAse-free tubes acquired from Gentra in Minneapolis, Minnesota.

T-ARMS PCR was used to detect VEGF single nucleotide gene polymorphism. To amplify the desired alleles, four primers were used: forward outer, reverse outer, forward inner, and reverse inner (Table 1). The PCR technique was done according to the method discussed by Hsieh et al. [15].

Genotyping of IL1b (-511) single nucleotide gene polymorphism by T-ARMS PCR:

Detection of VEGF single nucleotide gene polymorphism done by T-ARMS PCR. Four primers such as; forward outer, reverse outer, forward inner, and reverse inner were used to amplify the desired alleles (Table 1). PCR technique was done according to Pietrowski et al. [16].

Statistical Analysis:

All data was collected, processed, and statistically evaluated using IIBM SPSS Statistics for Windows, version 23.0 (IBM Corporation, Armonk, New York). Quantitative data was described using the mean, standard deviation, and range, whereas qualitative data was expressed using the number and %. The t-test was used to compare two groups of normally distributed variables. The Chi-square test or the Fisher exact test was used to compare percentages of categorical variables when applicable. The tests were all two-sided. Statistical significance was defined as a p-value < 0.05.

RESULTS

There was no variance in age, BMI, or marital status parameters between both groups ($p>0.05$). There was a remarkably higher percentage of positive family history of myoma, and irregular menses, in the fibroid group compared to the control ($p<0.05$), Also, the fibroid group signified with nulligravida and previous history of abortion ($p<0.05$). Regarding the site of leiomyoma; submucosal, intramural, and subserosal in patients were distributed as 68.6, 27.5, and 3.9%, respectively (Table 2).

A higher significant percentage of the VEGF-460 (TT) Gene Polymorphism was detected in the uterine leiomyoma group. There was one case that had a C homozygote uterine leiomyoma group compared to four healthy control groups. Percent of CC, CT, and TT for VEGF were 1.9/21.6/76.5% in the uterine leiomyoma group and 7.9/74.5/17.6% in the healthy control group. Allele (T) for the VEGF-460 gene was significantly dominant by (5.6 fold) in the UL group as compared with the healthy participant ($p=0.0001$) (Table 3).

The VEGF-460 (TT) Gene Polymorphism was significantly dominant (15.2 fold) in the UL group as compared with the control group ($p=0.0001$) (Table 4).

A higher significant percentage of the IL-1b (CC) Gene Polymorphism was detected in the uterine leiomyoma group. Three cases had TT homozygote in the uterine leiomyoma group compared to nine healthy control groups. Percent of TT, CT, and CC for IL-1b was 5.9/39.2/54.9% in the uterine leiomyoma group and 17.7/62.7/19.6% in the healthy control group. Allele (C) for the IL-1b gene was significantly dominant by (5 fold) in the UL group as compared with the healthy participant ($p=0.001$) (Table 5).

The IL-1b (CC) Gene Polymorphism was significantly dominant (5 fold) in the UL group as compared with the healthy participant (p=0.0001) (Table 6).

The combined "TT" VEGF-460 Gene Polymorphism and "CC" IL-1b polymorphism at position +511 was significantly dominant by (10.3 fold) in the UL group as compared with the control group (p=0.0001) (Table 7).

Table (1) Primers for VEGF-A rs 833061 (-460T>C) and IL1b (-511) Gene Polymorphism:

Direction	Primer sequence	PCR Product size
VEGF-A rs 833061 (-460T>C)		
FO	5'- CAAAGCCCATTCCCTCTTTA -3'	414 bp
RO	5'- CACAGCCTGAAAATTACCCA-3'	
FI C	5'- CGTGTGGGGTTGAGTGC - 3'	264 bp
RI T	5'- CTCCCCGCTCCACCA -3'	181 bp
IL1b (-511)		
FI	5'- TACCTTGGGTGCTGTTCTCTGCCGCA-3'	225 bp
RI	5'- GAGGCTCCTGCAATTGACAGAGAGCTAC-3'	294 bp
FO	5'- CCTGACAATCGTTGTGCAGTTGATGTCC-3'	464 bp
RO	5'- GCTCATCTGGCATTGATCTGGTTCATCC-3'	464 bp

Table (2) Demographic and clinical status of studied groups:

Parameters	Leiomyoma group (n=51)	Healthy Control Group (n=51)	χ 2 /t-test	p-value
Age per years Mean ±SD (range)	39.88±4.08 30-45	38.98±4.12 30-45	1.11	0.27
Body Mass index n(%) overweight obese	23(45.1%) 29(54.9%)	21(41.2%) 30(58.8%)	0.16c	0.69
Marital status n(%) married non	38(74.5%) 13(25.5%)	39(76.5%) 12(23.5%)	0.053c	0.818
Family history of myoma n(%) yes no	40(78.4%) 11(21.6%)	28(54.9%) ٢٣(45.1%)	**6.35c**	**0.012***
Menarche age per years Mean ±SD (range)	12.69±1.62 10-16	13.11±1.49 11-15	1.39	0.164
Regularity of menses Regular irregular	38(74.5%) 13(25.5%)	47(92.2%) 4(7.8%)	**5.72 c**	**0.017***
Reproductive history null gravida Yes	12(31.6%) 26(68.4%)	4 (10.3%) 35(89.7%)	**5.32c**	**0.021***
Previous abortion yes no	17(65.4 %) 9(34.6%)	12 (34.3%) 23(65.7%)	**5.78c**	**0.016***

Parameters	Leiomyoma group (n=51)	Healthy Control Group (n=51)	χ 2 /t-test	p-value
Contraceptive uses Yes	26(100)	35(100)	-	-
Site of uterine leiomyoma Submucosal Intramural Subserosal	 35 (68.6) 14 (27.5) 2 (3.9)	-	-	-
t: student 't, **χ 2: c** Chi-square test**, f:** Fisher exact test, *Data are expressed as mean ± standard deviation (SD), Range*, *P value ≥ 0.05: non-significant*				

Table (3) Frequency distribution of VEGF-460 Gene Polymorphism in Uterine leiomyomas patients and healthy control

GENETIC		Uterine leiomyoma group (n=51)	Healthy control group (n.51)	χ^2	p	Odds	95%CI	
							Upper	lower
VEGF-460 Gene Polymorphism	Gene frequency n(%)			35.4	.0001*			
	TT	39(76.5)	9(17.6)			17.33	1.72	174.3
	CT	11(21.6)	38(74.5)			1.16	0.11	11.45
	CC	1 (1.9)	4(7.9)			Ref		
Allele VEGF	Allele frequency n(%)							
	T	89(87.3)	56(54.9)	25.9	.0001*	5.6	2.8	11.3
	C	13(12.7)	46(45.1)			ref		
χ 2 Chi square test of significant, odds(odds ratio). 95%CI:95% confidence interval ,*p<0.05 significant p>0.05 no significant								

Table (4) Frequency distribution of "TT" VEGF-460 Gene Polymorphism in Uterine leiomyomas patients and healthy control

GENETIC		Uterine leiomyoma group n.51	Healthy control group n.51	χ^2	p	Odds	95%CI	
							Upper	lower
VEGF-460 Gene Polymorphism	Gene frequency n(%)							
	TT	39(76.5)	9(17.6)	35.42	.0001*	15.2	5.8	40
	CT+CC	12(21.6)	42(74.5)				Ref	
χ 2 Chi square test of significant, odds(odds ratio). 95%CI:95% confidence interval ,*p<0.05 significant p>0.05 no significant								

Table (5) Frequency distribution of IL-1b polymorphism at position +511 in uterine leiomyomas patients and healthy control

GENETIC		Uterine leiomyoma group n.51	Healthy control group n.51	χ^2	p	Odds	95%CI	
							Upper	lower
IL-1b polymorphism	Gene frequency n(%)			14.3	.001*			
Allele IL-1b	CC	28(54.9)	10(19.6)			8.4	1.88	37.4
	CT	20(39.2)	32(62.7)			1.87	0.45	7.76
	TT	3 (5.9)	9(17.7)			Ref		
	Allele frequency n(%)							
	C	76(74.5)	52(51.0)	12.07	.001*	2.8	1.6	5.1
	T	26(25.5)	50(49.0)			ref		

χ 2 Chi square test of significant, odds(odds ratio). 95%CI:95% confidence interval ,*p<0.05 significant p>0.05 no significant

Table (6): Frequency distribution of "CC" IL-1b polymorphism at position +511 in Uterine leiomyomas patients and healthy control

GENETIC		Uterine leiomyoma group n.51	Healthy control group n.51	χ^2	p	Odds	95%CI	
							Upper	lower
IL-1b gene polymorphism	Gene frequency n(%)							
	CC	28(54.9)	10(19.6)	13.59	.0001*	5	2.1	12.1
	CT+TT	23(45.1)	41(80.4)				Ref	

χ 2 Chi square test of significant, odds(odds ratio). 95%CI:95% confidence interval ,*p<0.05 significant p>0.05 no significant

Table (7): Frequency distribution of combined "TT" VEGF-460 Gene Polymorphism and "CC" IL-1b polymorphism at position +511 in Uterine leiomyomas patients and healthy control

"TT" VEGF-460 and CC IL-1b gene polymorphism	Uterine leiomyoma group n.51	Healthy control group n.51	χ^2	p	Odds	95%CI	
						Upper	lower
• \"TT" + CC	**Gene frequency n(%)**		**16.2**	**.0001***			
• **others**	**20(39.2)**	**3(5.9)**			**10.3**	**2.8**	**37.6**
	31(60.8)	**48(94.1)**				**Ref**	

χ 2 Chi square test of significant, odds(odds ratio). 95%CI:95% confidence interval ,*p<0.05 significant p>0.05 no significant

DISCUSSION

In premenopausal women, leiomyomas, often known as fibroids, are the most prevalent benign gynecological tumor. Leiomyomas have a significant financial impact, impacting an estimated 11 million women and costing the US economy 34 billion dollars a year. UL is among the most prevalent benign gynecological tumors that cause substantial mortality in women and are associated with a variety of problems [1]. Risk factors for the development of uterine leiomyomas include both controllable and non-modifiable factors [5].

The present study was carried out to give a better understanding of the genetic causes of uterine leiomyoma and predict the role of the polymorphism VEGF and IL1-b genes and uterine leiomyoma occurrence.

This was a comparative study conducted on a total of 102 patients who were allocated into two groups; 51 uterine leiomyoma patients with matched age and sex and 51 healthy females of reproductive age as a control group.

Regarding Family history, this study showed that; there was a marked higher percent of positive family history of myoma, and irregular menses, in the uterine leiomyomatios group compared to the healthy control ($p<0.05$), also, leiomyomatous group signified with nulligravida and previous history of abortion ($p<0.05$).

This is consistent with Saldana and colleagues' [17] findings that positive family history was substantially linked with a 20% greater chance of having UL in African-American women and a 30% increased risk in white women in our sample.

Likewise, in Japan, **Sato and his colleagues** [18] have displayed that; myomas in Japanese middle-aged women have a hereditary propensity to uterine myomas. Additionally, nulliparous women with a family history of myomas may be predisposed to the condition.

Regarding the Caucasian population, **Van Voorhis and his colleagues** [19] have reported that a maternal history of leiomyomas may be the most critical risk factor for the development of leiomyomas in a predominantly Caucasian population of women.

Regarding reproduction, According to the findings of our study, more than half of the participants sampled their gravida more than once. This research supported the findings of Laughlin et al. [20], who discovered that parity is inversely related to the likelihood of developing leiomyoma**.**

Several studies [21–23] have demonstrated that; UL are found in approximately 5-10% of infertile women. Furthermore, UL is the only abnormality diagnosed in 1-2.4% of infertile women.

Regarding menses, our study findings reveal that most of the study sample had early menarche at the age of (10-16) with a mean of 12.69 years and had regular periods.

This is consistent with the findings of Kim and Sefton's [24] study, which concluded that menarche at a young age increases the likelihood of developing UL and is also a risk factor for other hormonally induced diseases such as endometrial and breast malignancies.

It has been demonstrated that; Although they are frequently asymptomatic, UL can result in heavy menstrual bleeding, pelvic pain, and other symptoms that harm a woman's quality of life [25].

Lumsden and Wallace [26] reported that 30% of women had menorrhagia after myomectomy in their study with clinical signs of UL following myomectomy.

However, **Marino and his colleagues** [27] have demonstrated that After controlling for variables, the existence of a leiomyoma did not affect menstrual cycle length, flow length, or flow heaviness.

Regarding the distribution of leiomyoma sites; the current study demonstrated that Submucosal, Intramural, and Sub serosal in patients distributed as (68.6%),(27.5%),(and 3.9%), respectively.

While **Ngorili and his colleagues** [28] have demonstrated that; the prevalence of submucosal UL was 53.1 %, intramural fibroids 19.3%, subserosal fibroids 10.2% and other types 13.9%.

But, **Maitri** [29] who have demonstrated that; the prevalence of subserosal fibroids was 15.1% submucosal fibroids were 9.1%, and submucosal polyps 5.1% intramural fibroids 60%,

Allele (T) for the VEGF-460 gene was significantly dominant by (5.6 fold) in the uterine leiomyoma group as compared with the healthy participants ($p=0.0001$).

In this investigation, we discovered that the genotype distribution of VEGF in UL patients differed significantly from that of the general population. When compared to the healthy control group, the VEGF T homozygote and T allele are associated with a greater risk of UL generation ($p=0.0001$). The C allele and the heterozygote are linked to a reduced risk of UL formation.

This came in the same line with **Hsieh and his colleagues** [15] who have demonstrated that; The proportions of distinct VEGF polymorphisms in both groups were considerably different. The leiomyoma population had a greater prevalence of T homozygote and T allele. They have also reported that the 5-UTR–460 polymorphism in the VEGF gene might contribute to the pathogenesis of leiomyoma.

Ganapathy et al, have found that The VEGF gene polymorphism genotype distribution is -460 C> T; wild-type TT is 46.7%, but in our study, wild-type TT is roughly 17.6%. This disparity could be mainly attributed to ethnic variations between Asians and Caucasians [30].

Other scientists have demonstrated that variation in numerous cytokines influences genetic disease pathogenesis, susceptibility, and resistance. Allelic polymorphisms in a cytokine gene's regulatory or structural domain have been demonstrated to be significantly related to immunologic responses and the upregulation of the protein from the related gene. Susceptible genes are hypothesized to interact with other genes and the environment, promoting the growth of a certain disease. Interleukins and other cytokines have been found to play a role in the susceptibility to several gynaecological tumors [16].

We found that IL-1b gene polymorphism is linked to the development of UL, with a higher substantial proportion of the IL-1b (CC) Gene. There was polymorphism in the UL group.

In accordance, **Pietrowski and his colleagues** [16] have displayed that It was found that there was a substantial variation in the allele frequencies of the IL-1b-511 C<T polymorphism. Thus, they concluded that; The polymorphism of the IL-1b-511 promoter is linked to an elevated relevance to UL and, in addition, has a potential role in UL progression.

This is consistent with Mortezaee and his colleagues' [31] findings of TC polymorphism between the two populations. Our data suggest that the IL-1 â -511C>T promoter polymorphism impacts the risk of UL in our study women and that this polymorphism may be involved in the pathogenesis of UL.

The interaction between IL-1-511 genotypes and other peripheral variables could explain the disparities reported among examined groups. It is hypothesized that IL-1 gene polymorphism influences susceptibility to UL in populations exposed to specific peripheral stimuli [31].

A meta-analysis of the relationships between gastric cancer and IL-1b and IL-1 receptor antagonist gene polymorphisms validated these disparities between two Caucasian and Asian groups [32].

In contrast, Hsieh and colleagues [15] found no significant connection between UL prevalence in the Asian population and the polymorphism of IL1b-511 after analyzing identical polymorphisms of the interleukin-1b gene. This disparity could be attributed to the diverse genetic ethnicity of the studied cases. This discrepancy, for example, may suggest heterogeneity about specific genetic variants in Caucasian and Asian populations [33].

Our findings indicate a substantial connection between the IL-1B-511 allele and the development of UL, implying a probable genetic explanation for this frequent disorder. Our findings add to the expanding list of genetic factors that may enhance the risk of uterine leiomyoma. A more extensive study group with UL verified histopathologically and cases with no UL may be necessary to reach a final judgment about the role of the polymorphism of IL1-b-511 in cases with UL.

Despite the promising outcomes of the present study, the small sample size has been considered the main limitation. In addition, the single-based study made our results couldn't be generalized to the overall population. Further reports have to be conducted on a large number of cases in multicenter organizations

CONCLUSIONS

Patients with uterine leiomyoma were associated with a marked increase in both VEGF-460 (TT) and IL-1b polymorphism Gene Polymorphism compared to leiomyoma-free ones. Such outcomes were proved in all gene and allele frequencies. However, combined "TT" VEGF-460 Gene Polymorphism and "CC" IL-1b polymorphism at position +511 was significantly dominant in the uterine leiomyoma group as compared with the healthy control group

Conflicts of Interest

The authors report no conflicts of interest.

Funding Information

None declared

REFERENCES

1- Shoaieb AA, Fawaz MA, Abdel Fattah M. Socio-Demographic and Reproductive Health Profile Among Egyptian Women with Uterine Fibroid. Med. J. Cairo Univ. 2019;87:2369–77.

2- Clarke-Pearson DL, Geller EJ. Complications of hysterectomy. Obstet Gynecol. 2013;121:654–73.

3- Fischer NM, Nieuwenhuis TO, Singh B, Yenokyan G, Segars JH. Angiotensin-Converting Enzyme Inhibitors Reduce Uterine Fibroid Incidence in Hypertensive Women. J Clin Endocrinol Metab. 2021;106:e650–9.

4- Barjon K, Mikhail LN. Uterine Leiomyomata. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [cited 2023 Sep 9]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK546680/

5- Pavone D, Clemenza S, Sorbi F, Fambrini M, Petraglia F. Epidemiology and Risk Factors of Uterine Fibroids. Best Pract Res Clin Obstet Gynaecol. 2018;46:3–11.

6- Lee MJ, Yun BS, Seong SJ, Kim M-L, Jung YW, Kim MK, et al. Uterine fibroid shrinkage after short-term use of selective progesterone receptor modulator or gonadotropin-releasing hormone agonist. Obstet Gynecol Sci. 2017;60:69–73.

7- Commandeur AE, Styer AK, Teixeira JM. Epidemiological and genetic clues for molecular mechanisms involved in uterine leiomyoma development and growth. Hum Reprod Update. 2015;21:593–615.

8- Tal R, Segars JH. The role of angiogenic factors in fibroid pathogenesis: potential implications for future therapy. Hum Reprod Update. 2014;20:194–216.

9- Schlingemann RO, Van Noorden CJF, Diekman MJM, Tiller A, Meijers JCM, Koolwijk P, et al. VEGF levels in plasma in relation to platelet activation, glycemic control, and microvascular complications in type 1 diabetes. Diabetes Care. 2013;36:1629–34.

10- Rajuddin R, Oscar R, Dewi TP. Serum Vascular Endothelial Growth Factor Levels and Uterine Fibroid Volume.Indones J Obstet Gynecol. 2020;107–11.

11- Pietrowski D, Thewes R, Sator M, Denschlag D, Keck C, Tempfer C. ORIGINAL ARTICLE: Uterine Leiomyoma is Associated with a Polymorphism in the Interleukin 1-β Gene. Am J Reprod Immunol. 2009;62:112–7.

12- Church LD, Cook GP, McDermott MF. Primer: inflammasomes and interleukin 1β in inflammatory disorders. Nat Rev Rheumatol. 2008;4:34–42.

13- Smith AJP, Humphries SE. Cytokine and cytokine receptor gene polymorphisms and their functionality. Cytokine Growth Factor Rev. 2009;20:43–59.

14- Simonis-Bik AMC, Eekhoff EMW, Diamant M, Boomsma DI, Heine RJ, Dekker JM, et al. The heritability of HbA1c and fasting blood glucose in different measurement settings. Twin Res Hum Genet. 2008;11:597–602.

15- Hsieh Y-Y, Chang C-C, Tsai F-J, Lin C-C, Tsai C-H. T allele for VEGF-460 gene polymorphism at 5'-untranslated region is associated with higher susceptibility of leiomyoma. Biochem Genet. 2008;46:356–61.

16- Pietrowski D, Thewes R, Sator M, Denschlag D, Keck C, Tempfer C. Uterine leiomyoma is associated with a polymorphism in the interleukin 1-beta gene. Am J Reprod Immunol. 2009;62:112–7.

17- Saldana TM, Moshesh M, Baird DD. Self-reported family history of leiomyoma: not a reliable marker of high risk. Ann Epidemiol. 2013;23:286–90.

18- Sato F, Mori M, Nishi M, Kudo R, Miyake H. Familial aggregation of uterine myomas in Japanese women. J Epidemiol. 2002;12:249–53.

19- Van Voorhis BJ, Romitti PA, Jones MP. Family history as a risk factor for development of uterine leiomyomas. Results of a pilot study. J Reprod Med. 2002;47:663–9.

20- Laughlin SK, Schroeder JC, Baird DD. New directions in the epidemiology of uterine fibroids. Semin Reprod Med. 2010;28:204–17.

21- Cook H, Ezzati M, Segars JH, McCarthy K. The impact of uterine leiomyomas on reproductive outcomes. Minerva Ginecol. 2010;62:225–36.

22- Donnez J, Jadoul P. What are the implications of myomas on fertility? A need for a debate? Hum Reprod. 2002;17:1424–30.

23- Wallach EE, Verkauf BS. Myomectomy for fertility enhancement and preservation. Fertil Steril. 1992;58:1–15.

24- Kim JJ, Sefton EC. The role of progesterone signaling in the pathogenesis of uterine leiomyoma. Mol Cell Endocrinol. 2012;358:223–31.

25- Wise LA, Laughlin-Tommaso SK. Epidemiology of Uterine Fibroids – From Menarche to Menopause. Clin Obstet Gynecol. 2016;59:2–24.

26- Lumsden MA, Wallace EM. Clinical presentation of uterine fibroids. Baillieres Clin Obstet Gynaecol. 1998;12:177–95.

27- Marino JL, Eskenazi B, Warner M, Samuels S, Vercellini P, Gavoni N, et al. Uterine leiomyoma and menstrual cycle characteristics in a

population-based cohort study. Hum Reprod. 2004;19:2350–5.

28- Ngorili GS, Yadav BB, Takalkar AA. Epidemiological study of uterine fibroids: our experience from urban Maharashtra. Int J Reprod Contracept Obstet Gynecol. 2022;11:2101–5.

29- Kulkarni MR, Dutta I, Dutta DK. Clinicopathological Study of Uterine Leiomyomas: A Multicentric Study in Rural Population. J Obstet Gynaecol India. 2016;66(1): 412-6.

30- Ganapathy P, Devanatha Desikan Sheshadri V, Sarkar R, Jones S, Gunasekaran K, Feysia TO, et al. Vascular Endothelial Growth Factor Single Nucleotide Polymorphism +405 G/C (rs2010963) is associated with Levels, Infection Severity, and Amputation among South Indian Diabetic Foot Ulcer Patients. Evid Based Complement Alternat Med. 2023;2023:2059426.

31- Mortezaee FT, Chaleshtori MH, Kheiri S, Farrokhi E, Shariati L, Tabatabaiefar MA, et al. Interleukin-1 B Gene polymorphisms in Iranian Patients with Uterine Fibroid, A Case- Control Study. Biosci, Biotechnol Res Asia. 2015;12:341–5.

32- Camargo MC, Mera R, Correa P, Peek RM, Fontham ETH, Goodman KJ, et al. Interleukin-1beta and interleukin-1 receptor antagonist gene polymorphisms and gastric cancer: a meta-analysis. Cancer Epidemiol Biomarkers Prev. 2006;15:1674–87.

33- Schneider BG, Camargo MC, Ryckman KK, Sicinschi LA, Piazuelo MB, Zabaleta J, et al. Cytokine polymorphisms and gastric cancer risk: an evolving view. Cancer Biol Ther. 2008;7:157–62.

Citation

Abdelghany, M., Zidan, H., Mohamed Mowafy, H., ElShabrawy, S. Vascular Endothelial Growth Factor and Interleukin 1-b Gene Polymorphisms as a Genetic Predictor for Uterine Leiomyoma. *Zagazig University Medical Journal*, 2025; (479-488): -. doi: 10.21608/zumj.2023.235465.2882