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Relationship of Uterine Fibroids with Lipid Profile, Anthropometric Characteristics, Subcutaneous and Preperitoneal Fat Thickness

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Abstract

Background: Uterine fibroids (UFs) are the most common benign tumors of the uterus with an unknown etiology, affecting many women of reproductive age. We aimed to evaluate the association between UFs and anthropometric features, subcutaneous and preperitoneal fat thickness and lipid profile.

Methods: This is a case-control study conducted on 212 women who were available in the Al-Zahra specialized referral hospital from March 2018 to March 2019. Study variables including weight, height, waist and hip circumference were measured for all individuals. For patients with UFs, the size, number and location of fibroids were recorded. Also, subcutaneous and preperitoneal fat thicknesses were measured. Finally, the data were analyzed using the SPSS software ver.16.0

Results: The most common complaint was abnormal uterine bleeding (AUB) in both groups. Most of the patients had a body mass index (BMI) of 25–30. There were significant differences between the two groups in terms of age (P = 0.0001) and waist circumference (*P* = 0.011). Cholesterol levels were much higher in the case group. Only age and low-density lipoprotein-cholesterol (LDL-C) levels in the case group were positively related to developing UFs, such that with advancing aging and increasing levels of LDL-C, the likelihood of experiencing UFs rose by 10% and 1.1%, respectively. Also, there were no significant differences between the two groups regarding in either preperitoneal fat thickness (PFT) or subcutaneous fat thickness (SFT).

Conclusion: Our findings suggest that with aging and higher levels of LDL-C, the likelihood of developing UFs rises.

Keywords: Fatty tissue, Lipids, Skinfold thicknesses, Uterine fibroid

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Introduction

Uterine Fibroids (UFs) are the most common benign tumors in women of reproductive age with a prevalence ranging from 30%–70%. Fibroids present with a variety of symptoms including dysmenorrhea, heavy menstrual bleeding, anemia, pelvic pain and gastrointestinal complaints. Although the disease does not increase the mortality rate, it is assumed to be strongly associated with infertility and obstetrical complications. UFs are also the most common indication for hysterectomy in the United States.[1-4]

The etiology of UFs is still controversial; nevertheless, the pathogenesis of the disease is multi-factorial, including genetic mechanisms, cytokines, oxidative stresses and sex-steroid hormones.[5]

Many risk factors are believed to be associated with the high prevalence of fibroids (including age, hormonal contraceptives, race, early age of menarche, smoking). In recent years, obesity and its related indices (e.g. preperitoneal fat thickness [PFT], subcutaneous fat thickness [SFT], and lipid profile) have been investigated as important factors in predicting the development of UFs. However, various studies have reported different results.[4,6-11]

In the present study, we aimed to evaluate the relationship between anthropometric characteristics, lipid profile, and subcutaneous and PFT with UFs.

Materials and Methods

In this case-control prospective study, we enrolled 212 women of reproductive age who were available in the Al-Zahra governmental, specialized and referral hospital in Rasht, northern Iran, from March 2018 to March 2019 (for a period of one year).

All the data remains confidential and the results are reported as overall statistics without identifying any

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specific individual. Moreover, the patients were informed that they could leave the study at any time they wished throughout the duration of the project.

The inclusion criterion was having any obstetrical or gynecological complaints (e.g. dysmenorrhea, pelvic pain, abnormal uterine bleeding [AUB] and infertility). The exclusion criteria were: age under 15 years or above 50 years at the time of study, menopause, pregnancy, current or prior history of malignancies, positive medical history of cardiovascular, autoimmune or endocrine diseases (e.g. late menarche), family history of familial hyperlipidemia syndromes, being treated with lipid-lowering agents at the time the study and sonographic findings of adenomyosis.

The case group consisted of patients who had sonographic reports indicating UFs, while the control group included the ones without a past documented history of UFs. Case-control groups were adjusted for age and parity. The sample size of the study was calculated at a minimum of 108 patients in each group, with a confidence interval of 95% and 80% test power, based on the cholesterol indices reported in the study by Vignini et al.[12]

A detailed questionnaire was filled out by an obstetrician, gynecologist or a trained resident, for all the patients, eliciting the following information: age (years); age at menarche (years); oral contraceptive use; numbers of gestations, parities, abortions, live or dead babies; symptoms indicating UF (e.g. bleeding, abdominal or pelvic pain).

Anthropometric measurements were made by trained study personnel. Height was measured with a wall-mounted stadiometer and the patients' weight was measured on a calibrated balance beam scale (without shoes, with light dressing and in centimeters). Also, body mass index (BMI) was calculated according to BMI = body weight/height squared (kg/m^2) for the subjects.

All laboratory measurements were made at 08:00–09:00 AM, after an overnight fast, using standardized methods at the Al-Zahra hospital laboratory. Blood samples were obtained for fasting blood sugar (mg/dL), total cholesterol (mg/dL), triglyceride (mg/dL), high-density lipoprotein-cholesterol (HDL-C, mg/dL) and low-density lipoprotein-cholesterol (LDL-C, mg/dL).

Subsequently, all patients underwent abdominal or transvaginal sonography by a radiologist at Al-Zahra Medical Center, using a GE voluson (E6) model sonography device. With the patient lying in the supine position, PFT was measured as the fat deposition thickness from the surface of the liver to the linea alba. These measurements were provided using a 1 to 5 MHz convex probe (4C-A H46701AA; GE Healthcare Bio-Sciences), with a longitudinal scanning approach, positioned at the epigastrium perpendicular to the skin. With the same approach, the thickness of fat deposition between the skin and linea alba was also recorded to yield the SFT.[13]

For the patients in the case group, the size, number, and anatomical subtypes of UF (i.e. submucosal, subserosal and intramural) were measured and recorded.

Sample Size

The needed sample size was determined according to the cholesterol index based on the results of Vignini et al[12] with 95% confidence and 80% power and effect size 0.4. Thus, the calculated sample size was found to be 108 individuals in each group.

Statistical Analysis

All analyses were performed using SPSS software version 16.0. The variables were initially evaluated for normality using graphical method including probability plot and statistical tests including Kolmogorov-Smirnov. The assumption of homogeneity of variance was evaluated using Fisher exact test. To compare mean values in case of normal distribution of the data, parametric tests (e.g. independent *t* test) were applied, while for data with non-normal distribution, the Mann-Whitney test was used. To evaluate the relationship between qualitative variables, chi-square test or Fisher exact test were fitted. Effect size was estimated using Cohen's method.

A forward stepwise multiple logistic regression model was used to determine the odds ratio and to assess the independent relationships of predictive variables with the UFs. Those variables with *P* value less than 0.05 in univariate analysis were entered into the multivariate model. A *P* value <0.05 was considered as significant.

Results

In the present study, 212 patients who visited the obstetrics and gynecology clinic of Al-Zahra medical center of Rasht were enrolled. These patients were divided into two groups based on the diagnosis of UFs (104 with UF and 108 without UF). The most common chief complaint in both groups was AUB. The demographic features and basic obstetric history of the subjects are shown in Table 1. Most of the patients had a BMI of 25–30. There was a significant difference between the two groups regarding age and waist circumference, such that the subjects in the case group were older and had larger waist circumference values (Table 1).

As shown in Table 2, cholesterol levels were much higher in the case group, indicating a significant difference compared to the control group.

AUB was the most common complaint in patients with UFs. Furthermore, based on the sonographic imaging results, most of these UFs were either submucosal or intramural.

Multiple logistic regression models were fitted using the predictor variables which were found to be statistically significant (i.e. age, waist circumference, cholesterol and LDL-C levels) to test the research hypothesis regarding the relationship between presenting with UFs and predictor

Table 1. Characteristics of Cases With Uterine Fibroids and Controls

Characteristics		Cases (n = 104)	Control (n = 108)	*P* Value
Categorical Variables				
Chief complaint	AUB	76 (73.1)	72 (66.7)	0.014*
	Pain	22 (21.2)	16 (14.8)	
	Miscellaneous	6 (5.8)	20 (18.5)	
Hormonal contraceptive use	Yes	6 (5.8)	4 (3.7)	0.532**
	No	98 (94.2)	104 (96.3)	
Gravidity	0	9 (8.7)	17 (15.7)	0.238*
	1–2	52 (50)	54 (50)	
	3 and more	43 (41.3)	37 (34.3)	
Parity	0	11 (10.6)	21 (19.4)	0.142*
	1–2	69 (66.3)	69 (63.9)	
	3 and more	24 (23.1)	18 (16.7)	
Living child	0	11 (10.6)	20 (18.5)	0.207*
	1–2	70 (67.3)	70 (64.8)	
	3 and more	23 (22.1)	18 (16.7)	
Death child	0	101 (97.1)	108 (100)	0.116**
	1–2	3 (2.9)	0	
Abortion	0	67 (64.4)	74 (68.5)	0.493*
	1	27 (26)	21 (19.4)	
	2 and more	10 (9.6)	13 (12)	
BMI	<25	19 (18.3)	29 (26.9)	0.398*
	25–30	47 (45.2)	39 (36.1)	
	30–35	26 (25)	29 (26.9)	
	35>	12 (11.5)	11 (10.2)	
Quantitative Variables				
Age (y)		42.62 ± 6.22	38.00 ± 8.02	0.0001***
Height (cm)		160.21 ± 7.01	161.03 ± 5.80	0.120***
Weight (kg)		74.81 ± 13.18	73.48 ± 12.62	0.742***
Waist circumference (cm)		112.74 ± 12.68	108.54 ± 12.10	0.011***
Hip circumference (cm)		113.73 ± 11.83	111.18 ± 12.21	0.216***
Age at menarche (y)		13.53 ± 9.76	12.58 ± 1.51	0.767***

BMI, body mass index; AUB, abnormal uterine bleeding.
*Chi-square; **Fisher-exact test; *** Mann-Whitney.

Table 2. Lipid Profile in Case and Control Groups

Characteristics	Cases (n = 104)	Control (n = 108)	Effect Size	95% CI	*P* Value*
FBS (mg/dL)	94 (11.5)	94 (11)	0.06	-0.20–0.33	0.506
Cholesterol	174.5 (43.5)	164 (41)	-0.22	-0.49–0.03	0.023
TG	127.5 (66)	126 (76)	-0.04	-0.31–0.22	0.632
HDL-C	46 (15)	47 (12)	0.06	-0.20–0.33	0.746
LDL-C	92 (33)	91 (37.2)	-0.21	-0.48–0.05	0.047
Subcutaneous Fat Thickness (SFT)	16.55 (10.19)	18 (8.13)	-0.01	-0.28–0.25	0.572
Preperitoneal Fat Thickness (PFT)	14.32 (8.6)	14.3 (8)	0.08	-0.17–0.35	0.939

FBS, Fasting Blood Sugar; TG, triglyceride; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol.
Values are median (interquartile range); *Mann-Whitney.

variables. According to the results of the model, when compared to the control group only age and LDL-C levels in the case group were positively related to developing UFs, such that with advancing aging and increasing levels of LDL-C, the likelihood of experiencing UFs rose by 10% and 1.1%, respectively (Table 3).

Furthermore, as displayed in Table 4, no significant

Table 3. Association of Independent Predictor With Uterine Fibroids Using Forward Logistic Regression Model

	Odds Ratio	95% CI	*P* Value
Age (y)	1.09	1.05–1.14	0.001
LDL-C (mg/dL)	1.01	1.00–1.02	0.04

LDL-C, low-density lipoprotein-cholesterol.

Table 4. Relationship of Anatomical Site and Number of UFs With BMI and Waist Circumference

	No. of UFs		Anatomical Site of UFs	
	Single	Two and More	Submucosal and Intramural	Subserosal
BMI				
Normal	11 (16.7)	8 (21.1)	12 (17.6)	7 (19.4)
Overweight	31 (47)	16 (42.1)	34 (50)	13 (36.1)
Obese	16 (24.2)	10 (26.3)	12 (17.6)	14 (38.9)
Morbidly obese	8 (12.1)	4 (10.5)	10 (14.7)	2 (5.6)
P value*	0.924		0.072	
Waist circumference				
Under 88 cm	1 (1.5)	1 (2.6)	2 (2.9)	0
Over 88 cm	65 (98.5)	37 (97.4)	66 (97.1)	36 (100)
P value**	0.998		0.543	

BMI, body mass index; UFs, uterine fibroids.
*Chi-square; **Fisher exact test.

relationships were found between the number or anatomical site of fibroids and either BMI or waist circumference of the individuals.

Discussion

In the present study, we tried to evaluate the potential association between the anthropometric factors, lipid profiles, and central fat deposition (demonstrated by SFT and PFT) with the development of UFs. We found that age and higher levels of LDL-C are significantly related to greater risks of presenting with fibroids. In our study, the most common complaint was AUB, consistent with the findings of Huda et al[14] and Mahmood et al,[15] which might be the result of hormonal dysfunctions including estrogen levels.

Obesity is considered a major risk factor contributing to higher rates of UFs; however, different studies have shown various results due to different variables evaluated (e.g. central fat criteria or BMI). Some studies have found a significant relationship between BMI and waist circumference with UF rates,[7-9,16] while others have not.[17] These findings could be due to the fact that BMI, as well as anthropometric measures (e.g. weight, waist circumference) might not be a good indicator of fat distribution in the body. Therefore, sonographic indices like preperitoneal or SFT may provide an actual understanding of the central fat accumulation in an individual suffering from UF.[18,19] This finding is also important as it is now well understood that visceral fat is an active endocrine organ, producing hormones and, therefore, elevating the secretion of inflammatory mediators.[10,20] However, we did not obtain such results regarding the SFT or PFT values in our study, which might be the consequence of weight adjustment in our study (both groups were in the overweight range). On the other hand, in a study with a small sample size by Vignini et al., PFT was pronouncedly different between the case and control groups,[12] while SFT, BMI and waist/hip circumference ratio were not significantly related. However, in that study, it was reported that higher PFT measures were significantly associated with UFs, similar to our findings.[12] Ciavatti et al reported PFT as the single predictive variable related to UFs; however, unadjusted BMI and small sample size were the limitations of that study.[10]

We also investigated the effect of lipid profile criteria on UF, finding higher levels of cholesterol and LDL-C levels in the case group. Similar patterns were observed by Akinlua et al and Vignini et al.[12,21] On the other hand, Akinlua et al reported high levels of cholesterol and triglyceride in the case group. Vignini et al initially found a significant relationship between LDL-C levels and UFs. However, following multivariate regression analysis, only HDL-C was negatively related to UFs.[12,21] In contrast to these studies, Parazian et al and Ratch et al found no significant relationship between lipid profile and UFs, although it must be noted that both of them were retrospective studies.[18,22] In addition, Swarnaltha et al detected no significant difference regarding cholesterol and triglyceride levels between case and control groups.[19] There are also other studies, e.g. Sersam et al, which have found lower levels of LDL-C and total cholesterol and higher HDL-C values in patients with UFs.[23] Higher HDL-C levels were also reported in studies by Huda et al and Sadlonova et al for patients with UFs.[12,24] Sadlonova et al suggested that the higher HDL-C levels might have been due to the notable role of estrogen in development of UF, such that with higher levels of estrogen, a significant preventive effect of lipid profile, including lower LDL-C and higher HLD-C levels could be inevitable. However, this theory is still controversial and, therefore, the results could simply be due to small sample size or not-fully adjusted study population.[24]

Most of the studies (including ours), in which the subjects were adjusted for parity, have revealed no significant relationship between the two groups. The pathophysiology confirming the role of the number of gestations or labor on the preventive effects of UFs is not well determined; however, it is suggested that it might be

due the sensitivity of uterus to ischemia during labor.[23,25]

In the present study, age and waist circumference were found to be significantly higher in the case group, but age was the only factor that exerted a significant impact on the UF development with about 10% increased rate. The mean age of subjects was 42 years, compared to Huda et al who evaluated patients ranging from 30–39 years of age.[15] It is believed that in women of reproductive age, performing sonography could lead to detecting UFs in the age range of 30–40 years, which is in contrast to the findings of Lurie et al who identified the highest levels of UFs in women aged 40–60 years (33%).[26] That said, UFs in younger females could be due to positive genetic predisposition or race (e.g. African-Americans).[8]

Waist circumference was also evaluated in a study by Yang et al who found it to be significantly greater in patients with UFs compared to those without fibroids.[8] In addition, higher rates of metabolic syndrome were detected in such patients, suggesting that UFs might follow a similar pathogenesis as metabolic syndrome.[27]

In the present study, most of the patients had single intramural (or submucosal) fibroids. In a study by Naftalin et al, most of the fibroids were intramural, (57.8%) which is consistent with the results of our study, confirming the myometrium as the main source of UFs.[28]

Furthermore, there were no significant differences in fasting plasma glucose (FPG) levels between the two groups, while Yang et al, evaluating 615 patients, found the opposite, suggesting that hyperglycemia could be a major potential risk factor in this matter. Also, this finding could confirm the metabolic syndrome theory.[8]

Korkmaz et al reported a marked relationship between the number of UFs and lipid profile (triglyceride and LDL-C); however, the sample size of their study was relatively small.[29] Furthermore, Tak et al detected similar results; their findings indicate that by eliminating the "age" factor, in patients with three or more UFs, BMI, systolic blood pressure, lipid profiles, FPG, and triglyceride levels are relatively higher and HDL-C is rather lower, compared to women with a single UF.[27]

In conclusion, our findings indicate that with increasing age and higher levels of LDL-C, the likelihood of developing UFs rises.

Limitations and Strong Point

One of the limitations of our study could be the fact that we did not consider cytogenetics as a presumptive factor of developing UFs, probably reflecting a positive family history of UFs or chromosome 12 and 14 mutations. Moreover, we recommend future multi-centric studies with longer periods of evaluation.

One of the positive points of the present study is that to the best of our knowledge, there is only one similar study on visceral and peritoneal fat thickness, and this opens a possibility for further investigations.

Authors' Contribution

Study design: SHSH, SFDH; Data collection: SFA, FM; Data analysis: MSH; Drafting the manuscript: SFDH, SM, SK; Critically revising the manuscript: All authors. All authors have read the manuscript and approved its final version.

Conflict of Interest Disclosures

No potential conflict of interest relevant to this study was reported.

Ethical Statement

The study protocol was approved by the ethical committee of Guilan University of Medical Sciences with the code No.: IR.GUMS.REC.1396.510. Also, all the participants filled and signed informed consent forms based on the consent forms available at: ethics.research.ac.ir.

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