



## Original Article

# Association of Dyslipidemia with Uterine Fibroid: A Case Control Study

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### Abstract

**Background & objective:** Uterine fibroid (UF) is the most common gynaecological neoplasm. Despite the major public health impact of UF, little is known about their association. Some studies focused on the similarities between the common biological mechanisms underlying the development of UF and atherosclerotic plaques. So, it is possible to hypothesize that same atherogenic risk factors, such as dyslipidemia may play a role in UF pathogenesis. This study was carried out to investigate the lipid profile in patients with UF and to analyze the association of dyslipidemia with UF.

**Materials & Methods:** This case-control study was carried out in the outpatient and inpatient Department of Obstetrics & Gynaecology, BSMMU, Shahbag, Dhaka over a period of 12 months between March 2017 to February 2018. Participants were 100 in number and aged between 18 and 45 years. Cases consisted of 50 women with uterine fibroids diagnosed by ultrasonography attending the outpatient and inpatient department of obstetrics and gynaecology, BSMMU, having no previous hormonal treatment. A similar number of age matched women without UF visiting the same gynaecological outpatient clinic for routine reasons were recruited as controls. Women who were postmenopausal, pregnant, diagnosed cases of malignant diseases, diagnosed cases of hypertension, diabetes mellitus, thyroid disease, CLD and CKD and women undergoing hormonal therapy were excluded from the study. Fasting lipid profiles were determined in blood samples taken from each participant. Atherogenic index was also calculated. Chi-square test was used for testing statistical significance. Statistical significance was set at  $p < 0.05$ .

**Results:** Women with UF were found to have significantly higher levels of serum TC, TG and significantly lower level of HDL-C compared to the controls ( $p < 0.05$ ). The mean atherogenic index was  $4.30 \pm 1.41$  in case group and  $2.86 \pm 0.97$  in control group. The difference was statistically significant ( $p < 0.05$ ) between two groups.

**Conclusion:** There is an association between dyslipidemia and UF. Women with UF have higher atherogenic index compared to women without UF.

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### Introduction

Uterine fibroids (UF) are the most common benign tumors arising from the myometrium of the uterus,

also called uterine leiomyomas. Uterine leiomyoma are hormone dependent benign neoplasm of monoclonal origin.<sup>1</sup> They are

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typically found during middle and late reproductive years.<sup>2</sup> The incidence is about 60% in women under the age of 45, and 30% of the cases are symptomatic.<sup>3</sup> UF are frequently asymptomatic but can cause menstrual disorders, heavy menstrual bleeding, anemia, pelvic and/or back pain, and bowel disorders.<sup>4</sup> Moreover, UFs seem to be related to infertility and adverse obstetric events.<sup>5</sup> They are frequent indication for gynaecological surgery, most commonly hysterectomy and are considered a major public health concern.<sup>6,7</sup>

There are suggestions in the literature of a similarity between smooth muscle cells tumours (fibroids) and atherosclerotic plaque. Both conditions are of monoclonal in origin.<sup>8,9,10,11</sup> Cramer et al. suggested that excessive injury and repair of the endometrial lining of uterus may promote monoclonal expansion of smooth muscle cell population in the uterine wall, in a similar way to human atherosclerotic plaque.<sup>11</sup> Cells from these two conditions also behave identically in culture.<sup>11</sup>

High levels of cholesterol and triglycerides in the blood have been linked to atherosclerosis which increases the risk of heart diseases and stroke. If the growth of UF depends on atherogenesis hypothesis, then an analogous association of these risk factors should be observed. Atherogenic index of plasma is a novel index composed of TG and HDL. It has been used to quantify blood lipid levels. It is commonly used as optimal indicator of dyslipidemia and associated cardiovascular disease.

## Results

A total of 100 participants fulfilling the selection criteria and consenting to participate in the study were included. The analysis was done for case (n=50) and control (n=50).

Table I shows association of S. total cholesterol (TC) with uterine fibroids of the study subjects. It was observed that 27(54.0%) patients had raised TC in case group and 9(18.0%) in control group. The difference was statistically ( $p < 0.05$ ) significant in two groups. The Odds Ratio (OR) of developing fibroid with raised level of cholesterol is 2.85 fold higher than that in women with normal level of TC.

The primary aim of this study was to investigate the lipid profile in patients with UF and subsequently evaluate their possible association.

## Materials and Methods

This case-control study was carried out in the Outpatient and inpatient Department of Obstetrics & Gynaecology, BSMMU, Shahbag, Dhaka over a period of 12 months between March 2017 to February 2018. Participants were 100 in number and aged between 18 and 45 years. Cases consisted of 50 women with uterine fibroids diagnosed by ultrasonography attending the outpatient and inpatient department of obstetrics and gynaecology, BSMMU, having no previous hormonal treatment. A similar number of age matched women without fibroids visiting the same gynaecological outpatient clinic for routine reasons were recruited as controls. Women who were postmenopausal, pregnant, diagnosed cases of malignant diseases, diagnosed cases of hypertension, diabetes mellitus, thyroid disease, CLD and CKD and women undergoing hormonal therapy were excluded from the study. Fasting lipid profiles which included Serum Total Cholesterol (TC), High-Density Lipoprotein Cholesterol (HDL-C), Low-Density Lipoprotein Cholesterol (LDL-C), Triglycerides (TG) were determined in blood samples taken from each participant. Atherogenic index was also calculated. Chi-square test was used for testing statistical significance. Statistical significance was set at  $p < 0.05$ . The protocol of the study was approved by the ethical review committee of BSMMU.

**Table I: Association of serum total cholesterol with uterine fibroids (n=100)**

TC(mg/dl)	Case	Control	OR (Lower-Upper)	p value
	(n=50)	(n=50)		
	n(%)	n(%)		
Raised (>200)	27(54.0)	9(18.0)	2.85(2.10-3.86)	0.003 <sup>s</sup>
Normal (≤200)	23(46.0)	41(82.0)		

s= significant

p value reached from chi square test

Table II shows association of High-Density Lipoprotein Cholesterol (HDL-C) with uterine fibroids of the study groups. It was observed that significantly higher number of patients 28(56.0%) had low HDL-C in case group than in control group 13(26.0%). The Odds Ratio (OR) of developing fibroid with low level of HDL-C is 3.62 fold higher than that in women with normal level of HDL-C.

**Table II: Association of HDL-C with uterine fibroids (n=100)**

HDL-C (mg/dl)	Case	Control	OR (Lower-Upper)	p value
	(n=50)	(n=50)		
	n(%)	n(%)		
Low(<40)	28(56.0)	13(26.0)	3.62 (1.44-9.23)	0.001 <sup>s</sup>
Normal (≥40)	22(44.0)	37(74.0)		

s= significant

p value reached from chi square test

Table III shows association of High-Density Lipoprotein Cholesterol (HDL-C) with uterine fibroids of the study groups. It was observed that 26(52.0%) patients had raised LDL-C in case group and 6(12.0%) in control group. The difference was statistically ( $p<0.05$ ) significant in two groups. The Odds ratio of developing fibroid with raised LDL-C is 7.94 times higher than that in women with normal level of LDL-C.

**Table III: Association of LDL-C with uterine fibroids (n=100)**

LDL-C (mg/dl)	Case	Control	OR (Lower-Upper)	p value
	(n=50)	(n=50)		
	n(%)	n(%)		
Raised (≥ 130)	26(52.0)	6(12.0)	7.94(2.63-25.19)	0.001 <sup>s</sup>
Normal (< 130)	24(48.0)	44(88.0)		

s= significant

p value reached from chi square test

Table IV shows association of Triglycerides (TG) with uterine fibroids of the study groups. It was observed that 30(60.0%) patients had raised TG in case group and 13(26.0%) in control group. The difference was statistically ( $p<0.05$ ) significant in two groups. The risk of developing fibroid is 1.45 times higher in women with raised level of TG.

**Table IV: Association of TG with uterine fibroids (n=100)**

TG (mg/dl)	Case (n=50) n(%)	Control (n=50) n(%)	OR (Lower-Upper)	p value
Raised ( $\geq 150$ )	30(60.0)	13(26.0)	1.45 (0.6-3.52)	0.001 <sup>s</sup>
Normal ( $<150$ )	20(40.0)	37(74.0)		

s= significant

p value reached from chi square test

Table V shows comparison of lipid profile between two groups. It was observed that the mean total cholesterol (TC) was  $198.56\pm 34.94$  mg/dl in case group and  $165.52\pm 20.08$ mg/dl in control group. The mean total HDL-C was  $39.46\pm 10.51$ mg/dl in case group and  $44.92\pm 11.57$ mg/dl in control group. The mean total LDL-C was  $128.66\pm 32.86$  mg/dl in case group and  $101.42\pm 21.12$ mg/dl in control group. The mean total TG was  $173.8\pm 112.13$ mg/dl in case group and  $109.22\pm 51.73$  mg/dl in control group. The difference of TC, HDL-C, LDL-C and TG were statistically significant ( $p<0.05$ ) between two groups.

**Table V: Comparison of lipid profile in study groups (n=100)**

Lipid profile	Case (n=50) Mean $\pm$ SD	Control (n=50) Mean $\pm$ SD	p value
TC (mg/dl)	$198.56\pm 34.94$	$165.52\pm 20.08$	0.001 <sup>s</sup>
HDL-C (mg/dl)	$39.46\pm 10.51$	$44.92\pm 11.57$	0.015 <sup>s</sup>
LDL-C (mg/dl)	$128.66\pm 32.86$	$101.42\pm 21.12$	0.001 <sup>s</sup>
TG (mg/dl)	$173.8\pm 112.13$	$109.22\pm 51.73$	0.004 <sup>s</sup>

s= significant

p value reached from unpaired t-test

Table VI shows atherogenic index of the study groups. It was observed that the mean atherogenic index was  $4.30\pm 1.41$  in case group and  $2.86\pm 0.97$  in control group. The difference was statistically significant ( $p<0.05$ ) between two groups.

**Table VI: Comparison of atherogenic index in study groups (n=100)**

Atherogenic index	Case (n=50)	Control (n=50)	p value
Mean±SD	4.30 ±1.41	2.86 ±0.97	0.001 <sup>s</sup>
Range (Min,Max)	2.0, 7.71	1.38, 6.14	

s= significant

p value reached from unpaired t-test

The table VII shows the multiple logistic regression analysis done to see the effect of independent variables (serum cholesterol, triglyceride, HDL and LDL) on dependent variable (uterine fibroid). The increase in serum cholesterol increases the risk of developing fibroid by 2.82 fold and increased atherogenic index increases the risk by 3.32 fold.

**Table VII: Multiple logistic regression tables showing the effect of independent variables on dependent variable**

	B	S.E.	Wald	df	P value	OR	95% C.I	
							Lower	Upper
TC(mg/dl)	1.04	0.44	5.65	1	0.017 <sup>s</sup>	2.82	1.20	6.62
HDL-C(mg/dl)	0.14	0.10	1.78	1	0.182	1.15	0.94	1.40
LDL-C(mg/dl)	-0.07	0.04	3.68	1	0.055	0.93	0.87	1.00
TG(mg/dl)	-0.04	0.01	8.95	1	0.003	0.96	0.93	0.99
Atherogenic Index	1.20	0.44	7.41	1	0.007 <sup>s</sup>	3.32	1.40	7.88
Constant	29.825	10.559	7.979	1	0.005	3.950		

s= significant

B= coefficient for the constant.

S.E.=standard error around the coefficient for the constant.

Wald= Wald chi-square test that tests the null hypothesis.

df=This is the degrees of freedom for the Wald chi-square test

## Discussion

In this current study, it was observed that 54.0% patients had raised TC in case group and 18.0% in control group. TC was significantly ( $p < 0.05$ ) higher in patients with UF. The odds ratio (OR) of developing fibroid with raised TC had 2.85 (95% CI 2.10 to 3.86) times significantly higher than that in women with normal level of Total

cholesterol. Similar finding was observed by Kong et al.<sup>12</sup> According to their study total cholesterol (TC) (OR=6.70; 95% CI: 3.816-11.764) significantly increased the risk for uterine leiomyoma. Their study also suggested protective roles of higher level of HDL-C on uterine leiomyoma and supported the hypothesis that lower level of TC may reduce uterine leiomyoma

risk among premenopausal women. Cholesterol plays a significant role in the production of sex steroid. Estrogens are considered as promoters of uterine leiomyoma growth.<sup>4</sup>

In this present study, it was observed that 56.0% patients had low HDL-C in case group and 26.0% in control group. Low HDL-C was significantly ( $p < 0.05$ ) higher in patients with uterine fibroid. A subject with low HDL-C had 3.62 (95% CI 1.44 to 9.23) times significantly higher risk of developing fibroid than that in women with normal level of HDL-C. Vignini et al. mentioned that HDL-C maintained a significant correlation with the diagnosis of Uterine fibroid.<sup>13</sup> After adjustment by age, BMI and other potential factors, He et al. found a negative correlation between HDL-C and uterine leiomyoma in the hysterectomy-confirmed group.<sup>14</sup> Similar findings also observed by Kong et al. (2014).<sup>12</sup>

In this current study, it was observed that 52.0% patients had raised LDL-C in case group and 12.0% in control group. Raised LDL-C was significantly ( $p < 0.05$ ) higher in patients with uterine fibroid. A subject with raised LDL-C had 7.94 (95% CI 2.63 to 25.19) times increased risk to develop uterine fibroid. It was also observed that 60.0% patients had raised TG in case group and 26.0% in control group. Raised TG was significantly ( $p < 0.05$ ) higher in patients with UF. A subject with raised TG had 1.45 (95% CI 0.6 to 3.52) times increased risk to develop UF. Kong et al. reported that triglycerides might be associated with the onset of uterine leiomyoma.<sup>12</sup> There was another study by Takeda et al. who reported that women with uterine leiomyoma had significantly higher level of TG.<sup>15</sup> So, the result of the present study is consistent with these studies.

Regarding the lipid profile, Kong et al. reported that women with uterine leiomyoma had significantly higher levels of TC compared with control patients ( $4.71 \pm 0.91$  vs.  $4.14 \pm 0.84$ ,  $P < 0.05$ ).<sup>12</sup> Vignini et al. found a negative association between HDL-C values ( $45.4 \pm 8.3$  vs  $57.2 \pm 13.4$  mg/dL) and the presence of UF, whereas a positive association was found with LDL-C ( $92.3 \pm 21.5$  vs  $72.0 \pm 14.6$  mg/dL). The

investigators also showed no significant variation between cases and controls in serum total cholesterol and TG values.<sup>13</sup> Akinlua and Ojo, showed a raised level both cholesterol and triglycerides in fibroid patients ( $5.56 \pm 3.25$  mmol/L and  $1.14 \pm 0.61$  mmol/L) respectively compared with the non-fibroid patients ( $4.13 \pm 0.64$  mmol/L and  $0.5 \pm 0.51$  mmol/L) respectively.<sup>16</sup> Similar findings are also observed in our study.

Studies done by Sadlonova et al mainly discussed the effect of cholesterol on uterine leiomyoma incidence through the parameters of HDL-C, LDL-C and HDL-C/LDL-C.<sup>7</sup> The results were somewhat different in our study. However, Parazzini et al. did not observe an association between hyperlipidemia and fibroids. The study derived their data from medical records and subject interviews, moreover, the study contained no information on HDL-C, LDL-C or the atherogenic index.<sup>17</sup> Lin et al. also reported that plasma glucose and cholesterol had no relevance to the risk of uterine leiomyoma.<sup>18</sup> So, the results of these studies were not consistent with the current study.

In this present study, the mean atherogenic index was  $4.30 \pm 1.41$  in case group and  $2.86 \pm 0.97$  in control group. The mean atherogenic index was significantly ( $p < 0.05$ ) higher in patients with UF. Vignini et al. studies focused on the similarities between common biological mechanisms underlying the development of uterine fibroids and atherosclerotic plaques. Their study showed atherogenic index of plasma was found to be higher in cases than controls.<sup>13</sup> So, their study was consistent with the present study.

## Conclusion

Higher serum total cholesterol, TG, LDL-C and lower HDL-C are associated with higher risk of uterine fibroid (UF). Women with UF have higher atherogenic index compared to women without UF.

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