

## Association of Hyperglycemia, Hyperlipemia with the Risk of Uterine Leiomyomata: A Case-Control Study

Shujun Kong, Jianqing Hou\*, Min Xia, Ying Yang, Anli Xu, Qing Tang

*Department of Gynecology, Yantai Yuhuangding Hospital Affiliated of Medical College of Qingdao University, Yantai, 264000, Shandong, China*

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### Abstract

Uterine leiomyoma are common noncancerous tumors of the uterus and are the most frequent reason for recommending a hysterectomy. This study was conducted to investigate the associations between uterine leiomyoma and lifestyles including glucose metabolism, lipid metabolism and obesity. The case-control study was conducted from January 1st 2012 to December 31st 2012 at Yuhuangding Hospital in Yantai. All Uterine fibroid patients were confirmed by postoperative pathology. This case-control study composed of 165 cases and 165 controls. The adjusted odds ratio (OR) and 95% confidence interval (CI) were estimated using unconditional logistic regression. For premenopausal women, fasting plasma glucose (FPG) (OR=0.09; 95% CI: 0.003-0.029) and HDL-C/LDL-C (OR=0.01; 95% CI: 0.002-0.114) significantly decreased the risk of uterine leiomyoma. Conversely, total cholesterol (TC) (OR=6.70; 95% CI: 3.816-11.764) and body mass index (BMI) (OR=1.36; 95% CI: 1.226-1.517) significantly increased the risk. This study suggested protective roles for higher level of HDL-C and FPG on uterine leiomyoma, and supported the hypothesis that lower level of TC and BMI may reduce uterine leiomyoma risk among premenopausal women.

### 1. Introduction

Uterine leiomyoma, also known as leiomyomas,

are hormone-dependent benign neoplasm of monoclonal origin [1]. The incidence is about 60 % in women under the age of 45, and 30% of the cases are symptomatic [2]. Uterine leiomyomas

\* Corresponding author: [hjq63@126.com](mailto:hjq63@126.com)

women suffering from menstrual bleeding had symptoms including anemia, oppression of adjacent organs, pelvic pain and infertility. Although the etiology of Uterine leiomyoma remains unclear, estrogen is unequivocally associated with uterine leiomyoma growth [3]. It has been reported that the up-regulation of estrogen and its receptor can accelerate the growth of uterine leiomyoma [4]. Subcutaneous adipose tissue can produce a large number of estrogens. So far, there is no prospective evidence about influence of weight-loss on fibroid development. The close metabolic relationship between saccharide and lipids is manifested by the fact that both of their compounds are hydrocarbons. Therefore, we hypothesized that glucose metabolism, lipid metabolism and obesity may be involved in the pathogenesis of uterine leiomyoma.

## 2. Materials and Methods

### 2.1 Study Subjects

All subjects were genetically unrelated ethnic Han Chinese. The patients with uterine leiomyoma were recruited from the Department of Gynecology Department of Yuhuangding Hospital Affiliated to Qingdao University between January 1st 2012 and December 31st 2012 in Yantai City, Shandong Province. All uterine fibroid diseases were diagnosed by postoperative pathological examination. Patients were eligible to be included if they fulfilled these criteria: non-pregnancy premenopausal woman; newly histopathologically diagnosed uterine leiomyoma; no previous malignant tumors in other organs; no family history of tumor; no steroid drugs medication used during the last 12 months; without thyroid, liver and renal dysfunction (no symptoms of metabolic disorder). In total, 165 cases of uterine fibroid were enrolled. We operated on all patients via the hysterectomy or subtotal hysterectomy.

In total, 165 unrelated healthy individuals who received physical examination at Examination Center of Yuhuangding Hospital at the same time comprised the control group. Eligibility criteria for enrolment of the controls were: non-pregnancy

premenopausal woman; no history of cancer or any other serious chronic diseases; no family history of malignant or benign tumor; no steroid drugs medication used during the last 12 months; without thyroid dysfunction, liver and renal dysfunction (no symptoms of metabolic disorder); no individual history of hysterectomy or adnexectomy (including ovariectomy).

### 2.2 Methods

Considered estrogen is unequivocally associated with uterine leiomyoma growth and closely related to lipid metabolism, the study was designed to estimate glucose metabolism, lipid metabolism and incidence of uterine leiomyoma and to investigate risk factors. The adjusted odds ratio (OR) and 95% confidence interval (CI) were estimated using unconditional logistic regression.

### 2.3 Data Collection

The study project had been approved by the Medical Ethics Committee of Yuhuangding Hospital Affiliated to Qingdao University and was conducted according to the Declaration of Helsinki Principles. All participants in our study had signed an informed consent form. The data about demographic factors, height, weight, age at first menstruation, physical activities and disease history were interviewed by a trained research assistant using a standardized structured questionnaire. Body mass index (BMI) was calculated as body weight/square of height. Fasting plasma glucose (FPG), total cholesterol (TC), triglycerides (TG), LDL cholesterol and HDL cholesterol levels were measured in the two groups. After the interview a blood sample was collected from each study subject. All the blood samples in our study were detected by the same machine (Beckman DXC800 automatic biochemical analyzer).

### 2.4 Data Analysis

Chi-square and ANOVA were used to assess the differences in dichotomous variables and continuous variables between the cases and controls and to identify possible confounding

variables. The association between FPG, TC, TG, LDL-C, HDL-C, BMI and the risk of uterine fibroid was analyzed by calculating the adjusted odds ratios (OR) and 95% confidence intervals (95% CI). Statistical tests were considered to be significant if two-tailed p-value was less than 0.05. Statistical analysis was performed by SPSS statistical package (16.0; SPSS Inc. Chicago, Illinois).

### 3. Results

The distribution of demographic characteristics and uterine fibroid risk factors are presented in Table 1. Overall, 165 women with uterine fibroid and 165 cases in control group were recruited in this study. The distributions of age were similar in case and control groups ( $P=0.939$ ). The age of cases and controls were  $43.36\pm 6.74$  and  $43.47\pm 4.56$  respectively. Uterine fibroid group significantly differed from the control participants in FPG, TC, HDL, HDL-C/LDL-C and BMI. Controls tended to have higher FPG and HDL-C/LDL-C ( $5.10\pm 0.41$  vs.  $4.75\pm 0.41$ ,  $P=0.00$  and  $0.56\pm 0.06$  vs.  $0.48\pm 0.16$ ,  $P=0.00$ ). Women with uterine leiomyoma had significantly higher levels of TC and BMI compared with control patients ( $4.71\pm 0.91$  vs.  $4.14\pm 0.84$ ,  $P=0.014$  and  $24.63\pm 3.21$  vs.  $21.64\pm 3.29$ ,  $P=0.00$ ). The two groups did not differ significantly by Age, TG and LDL-C ( $P=0.939$ ,  $0.078$  and  $0.135$ ).

**Table 1 Comparison of clinical parameters between uterine leiomyoma and control group**

Variable	fibroids n=165	Controls n=165	F	P
Age/years	$43.36 \pm 6.74$	$43.32 \pm 4.54$	0.006	0.939
FPG/(mmol/L)	$4.75 \pm 0.41$	$5.10 \pm 0.41$	60.65	0.000
TC/(mmol/L)	$4.71 \pm 0.91$	$4.14 \pm 0.84$	34.79	0.014
TG/(mmol/L)	$0.99 \pm 0.49$	$0.86 \pm 0.31$	3.11	0.078
HDL-C/(mmol/L)	$1.39 \pm 0.33$	$1.61 \pm 0.32$	37.858	0.000
LDL-C/(mmol/L)	$3.05 \pm 0.93$	$3.21 \pm 0.68$	2.249	0.135
HDL-C/LDL-C	$0.48 \pm 0.16$	$0.56 \pm 0.06$	27.623	0.000
BMI/(kg/m <sup>2</sup> )	$24.63 \pm 3.21$	$21.64 \pm 3.29$	69.568	0.000

#### P for uterine leiomyoma vs. controls

The adjusted ORs and 95% CI for FPG, TC, TG, HDL-C/LDL-C, BMI and uterine fibroid are presented in Table 2. FPG and HDL-C/LDL-C

were inversely related to uterine leiomyoma, and OR were 0.09 (95% CI: 0.003-0.029;  $P=7.28\times 10^{-15}$ ) and 0.01 (95% CI: 0.002-0.114;  $P=6.22\times 10^{-5}$ ). Conversely, TC (OR=6.70, 95% CI: 3.816-11.764;  $P=4.12\times 10^{-11}$ ) and BMI (OR=1.36, 95% CI: 1.226-1.517;  $P=9.71\times 10^{-9}$ ) significantly increased the risk of uterine leiomyoma. And TG (OR =1.03, 95% CI: 0.95-1.45;  $P=0.60$ ) had no influences on the risk of uterine fibroid. Our data suggested that the level of FPG and HDL-C/LDL-C were negative correlative with the risk of uterine fibroid, and the level of TC and BMI were positive correlative with risk of fibroid.

**Table 2 Correlation between the variables and the risk of uterine leiomyoma**

Variable	P	OR	95% CI of OR
FPG	$7.28\times 10^{-15}$	0.09	0.003-0.029
TC	$4.12\times 10^{-11}$	6.70	3.816-11.764
TG	0.60	1.03	0.952-1.452
HDL-C/LDL-C	$6.22\times 10^{-5}$	0.01	0.002-0.114
BMI	$9.71\times 10^{-9}$	1.36	1.226-1.517
Constant	$1.25\times 10^{-4}$		

$\alpha =0.05$

### 4. Discussion

Uterine leiomyomata, clinically recognized in approximately 30% of reproductive-age women, are benign neoplasms arising from smooth muscle cells of the myometrium. The relation between FPG, TC, HDL-C/LDL-C, BMI and uterine leiomyomata has received limited research attention. The authors tested the hypothesis that FPG, TC, HDL-C/LDL-C and BMI can affect fibroid development by collecting detailed exercise information in a case-control study of uterine leiomyoma. On the basis of logistic regression analyses, FPG and HDL-C/LDL-C significantly decreased the risk of uterine leiomyoma. Conversely, TC and BMI significantly increased the risk (The results were presented in Table 2). All the data was derived from a case-control study, so bias should be considered. All the patients in the study met operational standard which meant that the volume of fibroid tissue was large enough or had caused serious symptoms. That may be one of the reasons

that differences between the two groups were more significant than other research [5].

In this study, we found that the high blood glucose might be a protective factor for uterine fibroid. We observed that women with the high blood glucose were less likely to develop uterine fibroid. The study about blacks also indicated that diabetes may play protective roles. However, the association of diabetes with uterine leiomyoma was weak for whites [6]. Vascular dysfunction is part of the pathogenesis of diabetes and could inhibit tumor development. Diabetes and Insulin resistance can be associated with cytotoxic effects from accompanying hyperglycemia and these factors could have direct antitumorigenic effects [6].

Our data showed that the total cholesterol (TC) level was an independent risk factor for uterine leiomyoma. Cholesterol plays a significant role in the production of sex steroid. Estrogens are considered as promoters of uterine leiomyoma growth [3]. By binding to ER- $\alpha$  and E receptor- $\beta$  (ER- $\beta$ ), Estrogens elicit its physiological effects on the target cells. Protein and mRNA expression levels of ER- $\alpha$  and ER- $\beta$  are higher in leiomyoma compared with normal myometrial. Estrogens and its receptors play a significant role in myometrial physiology and in uterine leiomyoma growth. Previous studies mainly discussed the effect of cholesterol on uterine leiomyoma incidence through the parameters of HDL-C, LDL-C and HDL-C/LDL-C. The study showed that women with uterine leiomyoma had outstanding higher levels of serum HDL-cholesterol than control patients (1.8 $\pm$ 0.3 vs. 1.6 $\pm$ 0.5;  $P$ <0.05). Women with uterine leiomyoma appeared significantly lower LDL-cholesterol levels compared with control patients (2.9 $\pm$ 0.7 vs. 3.4 $\pm$ 0.9;  $P$ <0.05) [7]. Some other studies also reported that plasma glucose and cholesterol had no relevance to the risk of uterine leiomyoma [5]. The reason caused this difference may be that the cases were selected from the physical examination data. And these cases were not confirmed by postoperative pathology and could not be ruled out other tumors. There was a certain bias simply inspected by B

ultrasonic. For example, it can't exactly distinguish the adenomyoma from the fibroid. Our data showed that the level of HDL-C of patients with uterine leiomyoma was lower than normal, but the level of LDL-C was not lower so much. And HDL-C/LDL-C of patients with uterine leiomyoma was lower than normal. That might be caused by that HDL-C transformed into pregnenolone or progesterone which might further transform into estrogens stimulating the growth of uterine leiomyoma. After adjustment by age, BMI and other potential factors, a study in the International Medical Center of PLA General Hospital in Beijing found a negative correlation between HDL-C and uterine leiomyoma in the hysterectomy-confirmed group [8]. This report is consistent with our conclusion. Few studies have investigated the mechanism of HDL-C decreased the risk of uterine leiomyoma.

Our data indicated that BMI was also an independent risk factor for uterine leiomyoma. Body mass and weight gain may increase the risk of uterine leiomyoma among premenopausal women. However, not all of the earlier studies supported this conclusion. The effects were more obvious for blacks than for whites, and the association was nonlinear [9-10]. The elevated risk of fibroid also had relevance to increased BMI in an Italian [11] and a Japanese study [12]. However, there was view that the conversion of androgens to estrogens occurring in peripheral fat tissue might not account for the association between uterine leiomyoma and BMI, because most of circulating estrogen in premenopausal women was derived from the ovaries. However, BMI was negative correlative with sex hormone binding globulin, so peripheral circulating androgen and estrogen might play higher biological activity in the obese women [13]. The elevated biological activity among the obese women could be counteracted by obesity-related anovulation. The data showed that there were no differences in height, but significant differences appeared in weight. Monitoring ovulation and detecting estrogens, androgen and sex hormone binding globulin may help to investigate the

mechanism that BMI accelerates uterine leiomyoma development in further research.

Triglycerides might be associated with the onset of uterine leiomyoma, but there were no differences in triglycerides between uterine leiomyoma patients and average people. There was also a study reported that women with uterine leiomyoma had significantly higher level of TG [12].

## 5. Conclusion

This study is the first epidemiologic research that precisely examined the association of plasma glucose, blood lipid and uterine leiomyoma risk in the world. In conclusion, our results supported that lower serum HDL-C level and higher total cholesterol level are associated with a higher risk of uterine leiomyoma in premenopausal women. It can be concluded that losing weight, adjusting the diet structure, lowering cholesterol level and elevating HDL-C level may reduce the risk of uterine leiomyoma.

Although uterine leiomyoma have been the leading indication for hysterectomy for decades, the epidemiological data on fibroid prevalence and risk factors are limited. Our study suggests that metabolic factor may play a role in fibroid development. However, our study is limited by the fact that the case is limited in number and are identified in our study by self-report. Further multicenter, large sample, long-term and prospective clinical trials are required to support current conclusions and so as to explore the exact radical mechanisms for the effects of hyperglycemia, hyperlipemia and fat on uterine leiomyoma.

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