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Relationship between Metabolic Syndrome and Uterine Leiomyomas: A Case-Control Study

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Key Words
Leiomyoma · Metabolic syndrome · Obesity · Hypertension · Hyperlipidemia · Hyperglycemia

Abstract
Background/Aims: Uterine leiomyomas are the most common gynecological benign tumor and greatly affect reproductive health and well-being. The pathophysiology and epidemiology of fibroids are poorly understood. Obesity and elevated blood pressure have been reported to be predisposing factors. In this study, we investigated whether fibroids are associated with some criteria of the metabolic syndrome. ***Methods:*** The case patients were 213 women who underwent hysterectomy or myomectomy for fibroids, and the control subjects were 159 women who underwent operation for benign indications other than fibroids. Preoperative information on body mass index (BMI), blood pressure (BP), serum triglyceride (TG) and fasting plasma glucose (FPG) was obtained from medical records. The patients were classified as overweight if they had a preoperatively measured BMI of ≥24.0, hypertensive if BP was ≥140/90 mm Hg, hypertriglyceridemic if TG was ≥150 mg/dl, and hyperglycemic if FPG was ≥110 mg/dl. ***Results:*** BMI, BP, TG and FPG were significantly higher in the case group compared with the control group. In logistic regression analysis, fibroids were statistically significantly associated with being overweight and hypertensive. With the combination of these risk factors, the risk of fibroids increased. ***Conclusion:*** Uterine leiomyomas may share pathogenic features with the development of metabolic syndrome.

Introduction

Uterine leiomyomas or fibroids are the most common gynecological benign myometrial neoplasms occurring in women of reproductive age [1]. These tumors are a major indication for hysterectomy in premenopausal women and annually account for 33% of all hysterectomies (over 200,000) in the United States [2, 3]. Although these benign tumors represent a significant health concern for women, the causes of uterine leiomyomas are unknown [4]. Epidemiological and experimental evidence has established an essential role of ovarian hormones in the pathogenesis of this disease. Numerous studies have shown that the growth of leiomyomas depends on the ovarian hormones estrogen (E_2) and progesterone [5]. Risk factors include age, African-American ethnicity, nulliparity, obesity and elevated blood pressure (BP) [6–8].

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It has been suggested that there are some factors that may be common between atheromatous plaque and uterine fibroids [9]. A key event in plaque formation is also smooth muscle cell proliferation. Uterine fibroids have a monoclonal origin, which has also been postulated in the formation of atheromatous plaques [10]. The cells from fibroids and atheromatous plaques behave identically in culture [11]. Moreover, a recent prospective study showed that elevated BP has an independent positive association with a risk of clinically detected uterine leiomyoma among premenopausal woman [8]. Elevated BP may cause smooth muscle cell injury and cytokine release and increase the risk of leiomyomas via a process analogous to atherosclerotic changes in arterial smooth muscle cells [7].

Recently the concept of a multiple risk factor-clustering syndrome, so-called metabolic syndrome, has been proposed as a highly atherogenic state independent of hypercholesterolemia [12]. This syndrome is a constellation of cardiovascular risk factors such as obesity, hypertension, hyperlipidemia and hyperglycemia. Metabolic syndrome induces cardiovascular disease by promoting atherosclerosis in arterial smooth muscle cells.

To further investigate the 'atherogenesis hypothesis of fibroids', we examined the relationship between metabolic syndrome and uterine fibroid risk.

Patients and Methods

The study was conducted using a sample of Japanese women between the ages of 40 and 49 years who were operated on between 1997 and 2005 at Osaka Medical Center for Cancer and Cardiovascular Diseases. Osaka is an industrial city in Japan. We recruited Japanese women who had regular menstrual cycles.

The case group consisted of women with histologically confirmed uterine fibroids. They underwent hysterectomy or myomectomy for the indication of symptomatic fibroids. They had no other gynecological disease. A total of 213 women (aged 40–49; median age 45 years) met these criteria.

The control group consisted of women who underwent operations for benign indications other than fibroids. Those who had symptomatic fibroids were excluded by checking the medical records. A total of 159 age-matched women (aged 40–49; median age 45 years) were included in the present study. They underwent conization for cervical intraepithelial neoplasm (105 cases), oophorectomy for benign adnexal tumors (44 cases), or transcervical resection for endometrial polyp (10 cases). The average age of the 2 groups was not significantly different (cases 44.8 ± 2.7 vs. controls 44.8 ± 2.7, p = 0.98).

Information on each patient's medical history, weight and height, BP, fasting plasma glucose (FPG) and serum triglyceride (TG) was obtained from the preoperative medical records. Body mass index (BMI) was calculated as weight/height^2. Risk factors for metabolic syndrome were defined as follows. Overweight or obesity was defined as a BMI of ≥24 kg/m^2 [11]. Hypertension was defined as a systolic BP of ≥140 mm Hg, a diastolic BP of ≥90 mm Hg, or current use of antihypertensive medications [12]. Hypertriglyceridemia was defined as a TG of ≥150 mg/dl and hyperglycemia was defined as a FPG of ≥110 mg/dl, according to the published criteria of metabolic syndrome for the Japanese population [13]. As we considered that fibroids potentially interfere with waist circumference, we did not use this criterion as a risk factor for metabolic syndrome.

The significance of differences between cases and controls was evaluated by Student's t test. Data are expressed as mean ± SD. Univariate and multivariate odds ratios (ORs) of the individual risk factors were calculated. The univariate OR of the risk of uterine fibroids was computed according to the number of risk factors of each subject. Statistical analysis was performed using Excel 2003 (Microsoft) with the add-in software Statcel 2 (OMS, Tokyo, Japan) and SPSS 11.0J (SPSS Inc., Chicago, Ill., USA). Statistical significance was set at $p < 0.05$.

Table 1. The average value of each risk factor

	Cases (n = 213)	Controls (n = 159)	p value
BMI	22.9 ± 3.0	21.5 ± 2.5	<0.0001
Systolic blood pressure, mm Hg	123.0 ± 22.7	114.0 ± 14.4	<0.0001
Diastolic blood pressure, mm Hg	75.1 ± 13.2	68.5 ± 10.6	<0.0001
TG, mg/dl	86.5 ± 47.4	72.6 ± 36.1	0.0023
FPG, mg/dl	93.2 ± 14.9	89.5 ± 8.0	0.0054

Results

Table 1 shows the comparison of clinical and biological parameters between the cases with uterine leiomyomas and controls. The average values of all risk factors were significantly higher in the case group than in the control group.

Comparison of the rate of abnormal findings for each risk factor of metabolic syndrome between the cases and controls is shown in table 2. The univariate and multivariate ORs are also shown in table 2. Using univariate analysis significant risk factors for uterine leiomyomas were overweight, hypertension and hypertriglyceridemia. In the multiple logistic regression analysis, overweight and hypertension were significant risk factors for leiomyoma.

We further investigated whether the cluster of risk factors (overweight, hypertension, hypertriglyceridemia

Table 2. Odds ratio of risk factors for uterine leiomyoma

Risk factors	Cases (n = 213)	Controls (n = 159)	Univariate odds ratio (95% CI)	p value	Multivariate odds ratio (95% CI)	p value
Overweight	64 (30.0%)	22 (13.8%)	2.68 (1.56–4.58)	0.0003	2.20 (1.25–3.86)	0.0061
Hypertension	31 (14.6%)	1 (0.63%)	5.52 (2.63–11.6)	<0.0001	4.90 (2.31–10.38)	<0.0001
Hypertriglyceridemia	21 (9.9%)	6 (3.8%)	2.79 (1.10–7.08)	0.0310	2.11 (0.79–5.61)	0.1353
Hyperglycemia	9 (4.2%)	2 (1.3%)	3.46 (0.74–16.3)	0.1154	2.55 (0.50–13.03)	0.2605

Table 3. Comparison between cases of uterine leiomyoma and controls regarding the number of risk factors and the odds ratio of multiple risk factors for metabolic syndrome

Number of risk factors	Cases (n = 213)	Controls (n = 159)	Univariate odds ratio (95% CI)	p value
0	109 (51.1%)	126 (79.2%)	0.27 (0.17–0.44)	<0.0001
1	71 (33.3%)	27 (17.0%)	2.44 (1.48–4.04)	0.0005
2	26 (12.2%)	6 (3.8%)	3.19 (2.00–5.10)	<0.0001
3	7 (3.3%)	0 (0%)	3.64 (2.28–5.82)	<0.0001

and hyperglycemia) contributed to the risk of uterine leiomyomas. The number of risk factors was compared between the case and control groups (table 3). As there were no patients who had all the risk factors, we compared the number of risk factors ranging from 0 to 3. The number of risk factors was significantly higher in the case group than in the control group ($p < 0.0001$, Mann-Whitney's U test). The risk of fibroids was increased with the combination of these risk factors; the ORs for 0, 1, 2 and 3 risk factors were 0.27, 2.44, 3.19 and 3.64, respectively.

Discussion

This is the first report on the relationship between metabolic syndrome and uterine leiomyomas. Table 1 shows that subjects who had clinically symptomatic uterine leiomyomas had significantly higher BMI, BP, serum TG and FPG than control subjects. The data about BMI and BP are consistent with previous reports showing that obesity and hypertension were risk factors for uterine leiomyoma [6, 7]. To our knowledge, there have been no reports about the serum TG and FPG levels of patients with uterine leiomyomas so far.

According to the multiple logistic regression analysis results in table 2, overweight and hypertension were significant risk factors for leiomyoma. Though hypertriglyceridemia and hyperglycemia were not significant risk factors, these two factors seemed to contribute to the leiomyoma to some extent. Metabolic syndrome is a constellation of cardiovascular risk factors such as obesity, hypertension, hyperlipidemia and hyperglycemia. As our data showed that the risk of fibroids was increased with the combination of these risk factors, metabolic syndrome could be a risk factor for fibroids.

Though waist circumference is used for the index of abdominal adiposity in the diagnosis of metabolic syndrome [10], we have no data about this. As the abdomen of the women with fibroids is enlarged by the uterus, we could not evaluate the visceral fat accumulation with waist circumference. It has been reported previously that high percent body fat analyzed by electrical impedance could be a risk factor for uterine leiomyomas [14]. Evaluating the visceral fat accumulation might further support a relationship between metabolic syndrome and uterine leiomyomas.

Reasonable next steps of our research are to conduct a clinical trial to investigate the change in fibroid size among women treated for metabolic syndrome compared with those not treated. This research could provide novel approaches to explore the medical management of uterine leiomyomas.

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