Evaluation of Cardiovascular Risk Factors in Women with Uterine Leimyoma: Is There a Link with Atherosclerosis?

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ABSTRACT

Objective: Both uterine leimyoma (UL) and cardiovascular disease are public health problems affecting women at different age ranges. Smoking, obesity, and hypertension have been shown to be associated with UL in different random studies. However cardiovascular risk factors have not been evaluated systematically in patients with UL. Accordingly, we aimed to evaluate the cardiovascular risk factors and their relation with the presence of UL.

Material and Methods: One hundred and eighty nine patients with the pathological diagnosis of UL and one hundred and eighty nine age matched control subjects without UL were retrospectively included in the study from our data base of the pathology and gynecology departments. Controls were patients with intact uteri who had visited the same physicians for a routine checkup that included a pelvic examination and uterine sonogram and without mention of physical findings consistent with UL. The following clinical and demographic parameters were recorded; age, sex, hypertension, diabetes mellitus, and hypercholesterolemia. Current cigarette smoking was defined as active smoking within the past 12 months.

Results: Comparison of cardiovascular risk factors between with and without UL revealed that the presence of hypertension (80 (42.3%) vs 53 (28%) p=0.004) diabetes mellitus (33 (17.4%) vs. 16 (8.4%) p=0.009), smoking (31 (16.4%) vs. 11 (5.8%) p=0.001), were significantly higher in patients with UL than in control subjects. The mean-age and presence of hyperlipidemia were comparable between the two groups. Logistic regression analysis revealed an independent and positive association of UL with the presence of hypertension (odds ratio 2.02 CI: 1.25-3.27 p=0.004), diabetes mellitus (odds ratio 2.43 CI: 1.23-4.79 p=0.010), and smoking status (odds ratio 3.46 CI: 1.65-7.22 p=0.001).

Conclusion: We have shown that major cardiovascular risk factors namely, hypertension, diabetes mellitus and smoking are significantly and independently associated with UL. Our findings highlight the possible association of UL with atherosclerosis.

Key Words: Atherosclerosis, cardiovascular risk factors, hypertension, diabetes mellitus, smoking, uterine leimyomata (UL)

Introduction

Uterine leiomyomata (UL) (also known as fibroids or myomas) are the most common pelvic neoplasms in women (1-3). Epidemiologic studies demonstrate that these hormone dependent, benign tumors follow a woman's reproductive life cycle, increasing in risk with age up until the fifth decade, followed by a precipitous decline at menopause (4, 5). Although these benign tumors represent a significant public health concern, the epidemiology of uterine leiomyomata is poorly understood. The true population prevalence of fibroids, however, is probably underestimated because of the unknown distribution of subclinical tumors (3). Studies screening randomly selected women using ultrasonography or pathologic examination of uteri have reported uterine leiomyomata prevalence values ranging from 5.4 to 77 percent (6-9).

Although the risk of UL decreases at menopause, the risk of coronary artery disease increases after menopause. Both the UL and cardiovascular disease are public health problems affecting women at different age ranges. Smoking, obesity, and hypertension have been shown to be associated with UL in different random studies (1, 10, 11). However, cardiovascular risk factors have not been evaluated systematically in patients with UL. Accordingly, we aimed to evaluate the cardiovascular risk factors and their relation with the presence of UL.

Material and Methods

One hundred and eighty nine patients with a pathological diagnosis of UL and one hundred and eighty nine age matched control subjects without UL were retrospectively included in the study from our data base of the pathology and gynecology department. Controls were patients with intact uteri who had visited the same department for a routine check-up or complaints of pelvic pain, dysuria, poly-or dys-menorrhea, anemia, and infertility that included a pelvic examination, and uterine sonogram. Control subjects had no UL proven by uterine sonography. The following clinical and demographic parameters were recorded; age, sex, hypertension (known hypertension

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treated with antihypertensive drugs, two or more blood pressure recordings greater than 140/90 mm Hg), diabetes mellitus (known diabetes treated with diet or drugs or both; or either a fasting serum glucose of more than 126 mg/dL), hypercholesterolemia (known treated hypercholesterolemia or fasting or non-fasting serum cholesterol concentrations higher than 200 mg/dL). Current cigarette smoking was defined as active smoking within the past 12 months.

Patients with hepatic or renal failure, polycystic ovarian syndrome, malignancies and other systemic disease were not included in the study.

Statistical Analysis

Results are expressed as the mean±SD and percents. The differences between the two groups were tested for significance by chi-square and independent samples t-tests where suitable. Differences were considered significant at $p<0.05$. We investigated the association of different variables on UL using logistic regression analysis. Parameters, namely, age gender, presence of hypertension, hyperlipidemia, diabetes mellitus, smoking status, and family history of coronary artery disease were included in the analysis. Statistical analyses were performed by using SPSS 15.0 Statistical Package Program for Windows (SPSS Inc., Chicago, Illinois, USA).

Results

Patients and control subjects' baseline characteristics are presented in Table 1. Comparison of cardiovascular risk factors between two groups revealed that presence of hypertension (80 (42.3%) vs. 53 (28%) p=0.004) diabetes mellitus (33 (17.4%) vs. 16 (8.4%) p=0.009), smoking (31 (16.4%) vs. 11 (5.8%) p=0.001). Age and presence of hyperlipidemia were comparable between the two groups (Table 1). Logistic regression analysis revealed an independent and positive association of UL with the presence of hypertension (odds ratio 2.02 CI: 1.25-3.27 p=0.004), diabetes mellitus (odds ratio 2.43 CI: 1.23-4.79 p=0.010), and smoking status (odds ratio 3.46 CI: 1.65-7.22 p=0.001, Table 2).

Discussion

Leiomyomas are the most common female reproductive tract tumors. They are probably of unicellular origin (12). Although studies have not clarified the exact process, uterine fibroid tumors arise during the reproductive years and tend to enlarge during pregnancy and regress after menopause. The documented risk factors for uterine fibroids are, black race, family history of uterine fibroids, age >40 years, nulliparity, obesity, and hypertension (1, 13, 17).

The main finding of our study is that cardiovascular risk factors namely, hypertension, diabetes mellitus, and smoking have been found to be independently and positively associated with uterine fibroids. Since age was matched for control subjects, only hyperlipidemia among the cardiovascular risk factors is independent of uterine fibroids.

Coexistence of hypertension with UL has been documented in several small studies (10, 16-20). Boynton-Jarrett

et al.(11) has reported the first prospective data demonstrating a dose response relation between diastolic blood pressure and fibroid incidence, with higher blood pressure associated with higher fibroid risk. The association of UL with hypertension has been explained partially by the reverse-causality interpretation suggesting that UL may cause hypertension as a consequence of urinary tract obstruction by large tumors (10, 20). Another explanation has been made by the renin-angiotensin system, which is implicated in the pathogenesis of hypertension (21-23). Angiotensin II (AT-II) has a proliferative action in that it stimulates the hypertrophy of cardiac and vascular smooth muscle (21, 23). AT-II receptor expression has also been shown in various tissues, including the uterine myometrium and vascular smooth muscle cells (24). Local expression of these factors, such as transforming growth factor β and platelet derived growth factor, are postulated to be critical to the growth of leiomyomata as well (25, 26). In accordance with previously published literature, hypertension has been found to be independently associated with UL with a relatively high odds ratio of 2.02 (CI: 1.25-3.27).

In addition to hypertension, we have also found that the presence of diabetes mellitus is an independent factor for UL with an odds ratio of 2.43 (CI: 1.23-4.79). Although it did not have statistical significance, a pattern similar to the association of UL with hypertension was observed by Faerstein et al. (18). Higher proportions of cases had more severe diabetes, were younger at diabetes diagnosis, and had diabetes of longer duration. To the best of our knowledge, this is the first report documenting an independent association between diabetes mellitus and UL. Indeed, it is reasonable to expect such an effect of diabetes mellitus on UL formation. Effects of diabetes mellitus on progression of atherosclerosis have been shown by the demonstration of increased carotid artery intima-media thickness (27, 28). Diabetes mellitus is known to

Table 1. Comparison of patient with myoma uteri and control subjects

Variables	Myoma Uteri (n=189)	Control Subjects (n=189)	p value
Age (Years)	45±9	45±8	0.94
Hypertension	80 (42%)	53 (28%)	0.04
Diabetes Mellitus	33 (17%)	16 (8%)	0.09
Hyperlipidemia	31 (16%)	22 (11%)	0.18
Smoking	31 (16%)	11 (5%)	0.01

Table 2. Logistic regression analysis

Variables	Odds ratio	Confidence interval	p value
Age	0.98	0.95-1.00	0.184
Hypertension	2.02	1.25-3.27	0.004
Diabetes Mellitus	2.43	1.23-4.79	0.010
Hyperlipidemia	1.51	0.82-2.79	0.186
Smoking	3.46	1.65-7.22	0.001

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promote negative remodeling in the arterial wall and impair compensatory arterial enlargement during the course of the atherosclerotic process (29, 30). Hyperinsulinemia is a good candidate for UL formation by means of myometrial smooth muscle cell proliferation and/or increasing circulating levels of ovarian hormones. Insulin resistance and hyperinsulinemia have been proposed as possible mechanisms underlying pathophysiologic pathways connecting obesity, diabetes, hypertension, and hyperlipidemia, eventually leading to atherosclerosis (31). Additionally, insulin has been shown to promote cell mitosis, to promote vascular smooth muscle proliferation, and in particular, to stimulate the growth of UL cells in tissue culture (32-34). Insulin may have also a specific gonadotropic function, stimulating ovarian secretion via insulin receptors or receptors for insulin-like growth factors (35).

On the contrary, in previous literatures in which smoking has been reported as a negative risk factor, we have found that smoking is positively and independently associated with UL formation. Smoking has been reported to reduce the risk of UL in several studies (1, 8, 36, 37). No statistically significant associations have been observed between cigarette smoking variables and UL risk. On the other hand, smoking for more than 19 years is associated with a 40 percent decreased risk of UL (18). Although smoking is considered to be associated with an estrogen-deficient state which is supposed to be an underlying reason for less frequent UL in smokers in published literature, smoking is one of the major risk factor for atherosclerosis (38). A common key element of atherosclerosis and UL is smooth muscle cell proliferation. Recent epidemiological studies have shown that smoking is a significant and independent risk factor for cardiovascular disease, and peripheral vascular disease (39, 40). Nicotine, a major constituent of tobacco, is known to be directly involved in smooth muscle cell proliferation (41). UL has a monoclonal origin, which has also been postulated for the atheromatous plaque; cells from both conditions behave identically in culture (42-44). In terms of smooth muscle cell proliferation, it is reasonable to expect a positive association with smoking and UL.

Conclusion

We have shown that major cardiovascular risk factors, namely, hypertension, diabetes mellitus and smoking are significantly and independently associated with UL. Our findings highlight the possible association of UL with atherosclerosis. Therefore, further studies are needed to elucidate the role of cardiovascular risk factors or atherosclerosis in the pathogenesis of UL or vice versa.

Conflict of Interest
No conflict of interest was declared by the authors.

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