

1 Evaluation of Cardiovascular Risk Factors in Women with Uterine Leimyoma: Is there a Link
2 with Atherosclerosis?
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19 Running Title: Uterine leimyoma and cardiovascular risk factors
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Abstract:

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

Materials and Methods:

One hundred and eighty nine patients with 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 pathology and gynecology department. 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 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 control subjects. The mean-age and presence of hyperlipidemia were comparable between two groups (table-I). 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 leiomyomata (UL)

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72 Introduction

73 Uterine leiomyomata (UL) (also known as fibroids or myomas) are the most common
74 pelvic neoplasm in women¹⁻³. Epidemiologic studies demonstrate that these hormone
75 dependent, benign tumors follow a woman's reproductive life cycle, increasing in risk with
76 age up until the fifth decade followed by a precipitous decline at menopause^{4,5}. Although
77 these benign tumors represent a significant public health concern, the epidemiology of uterine
78 leiomyomata is poorly understood. The true population prevalence of fibroids, however, is
79 probably underestimated because of the unknown distribution of subclinical tumors³. Studies
80 screening randomly selected women using ultrasonography⁶⁻⁸ or pathologic examination of
81 uteri⁹ have reported uterine leiomyomata prevalence values ranging from 5.4 to 77 percent.

82 Although the risk of UL decreases at menopause, risk of coronary artery disease
83 increases after menopause. Both the UL and cardiovascular disease are the public health
84 problem affecting the women at different age ranges. Smoking, obesity, and hypertension has
85 been shown to be associated with UL in different random studies^{1,10,11}. However
86 cardiovascular risk factors have not been evaluated in patients with UL systematically.
87 Accordingly we aimed to evaluate the cardiovascular risk factors and their relation with the
88 presence of UL.

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90 Materials and Methods:

91 One hundred and eighty nine patients with pathological diagnosis of UL and one hundred and
92 eighty nine age matched control subjects without UL were retrospectively included in the
93 study from our data base of pathology and gynecology department. Controls were patients
94 with intact uteri who had visited the same department for a routine check-up or complaints of
95 pelvic pain, dysuria, poly-or dys-menorrhea, anemia, and infertility that included a pelvic
96 examination, and uterine sonogram. Control subjects had no UL proven by uterine
97 sonography. The following clinical and demographic parameters were recorded; age, sex,
98 hypertension (known hypertension treated with antihypertensive drugs, two or more blood
99 pressure recordings greater than 140/90 mm Hg), diabetes mellitus (known diabetes treated
100 with diet or drugs or both; or either a fasting serum glucose of more than 126 mg/dl),
101 hypercholesterolemia (known treated hypercholesterolemia or fasting or non-fasting serum

102 cholesterol concentrations higher than 200 mg/dl). Current cigarette smoking was defined as
103 active smoking within the past 12 months.

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

106 Statistical Analysis:

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

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116 Results:

117 Patients and control subjects' baseline characteristics are presented in table-I. Comparison of
118 cardiovascular risk factors between two groups revealed that presence of hypertension (80
119 (42,3%) vs 53 (28%) $p=0,004$) diabetes mellitus (33 (17,4%) vs 16 (8,4%) $p=0,009$), smoking
120 (31 (16,4%) vs 11 (5,8%) $p=0,001$). Age and presence of hyperlipidemia were comparable
121 between two groups (table-I). Logistic regression analysis revealed an independent and
122 positive association of UL with the presence of hypertension (odds ratio 2,02 CI: 1,25-3,27
123 $p=0,004$), diabetes mellitus (odds ratio 2,43 CI: 1,23-4,79 $p=0,010$), and smoking status (odds
124 ratio 3,46 CI: 1,65-7,22 $p=0,001$,table II).

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127 Discussion

128 Leiomyomas are the most common female reproductive tract tumors. They are
129 probably of unicellular origin¹². Although studies have not clarified the exact process, uterine
130 fibroid tumors arise during the reproductive years and tend to enlarge during pregnancy and
131 regress after menopause. The documented risk factors for uterine fibroids are black race,
132 family history of uterine fibroids, age >40 years, nulliparity, obesity, and hypertension^{1,13-17}.

133 The main finding of our study is that cardiovascular risk factors namely, hypertension,
134 diabetes mellitus, and smoking have been found to be independently and positively associated

135 with uterine fibroids. Since age was matched for control subjects, only hyperlipidemia among
136 the cardiovascular risk factors is independent of uterine fibroids.

137 Coexistence of hypertension with UL has been documented in several small
138 studies^{10,16-20}. Boynton-Jarrett et al¹¹ has reported the first prospective data demonstrating a
139 dose response relation between diastolic blood pressure and fibroid incidence, with higher
140 blood pressure associated with higher fibroid risk. The association of UL with hypertension
141 has been explained partially by the reverse-causality interpretation suggesting that UL may
142 cause hypertension as a consequence of urinary tract obstruction by large tumors^{10,20}. Another
143 explanation has been made by renin-angiotensin system which is implicated in the
144 pathogenesis of hypertension²¹⁻²³. Angiotensin II (AT-II) has a proliferative action in that it
145 stimulates the hypertrophy of cardiac and vascular smooth muscle^{21,23}. AT-II receptor
146 expression has also been shown in various tissues, including the uterine myometrium and in
147 vascular smooth muscle cells²⁴. Local expression of these factors, such as transforming
148 growth factor β and platelet derived growth factor, are postulated to be critical to the growth
149 of leiomyomata as well^{25,26}. In accordance with previously published literature, hypertension
150 has been found to be independently associated with UL with a relatively high odds ratio of
151 2,02 (CI:1,25- 3,27).

152 In addition to hypertension we have also found that presence of diabetes mellitus is an
153 independent factor for UL with an odds ratio of 2,43 (CI:1,23-4,79). Although it did not have
154 statistical significance, a pattern similar to the association of UL with hypertension was
155 observed by Faerstein et al¹⁸. Higher proportions of cases had more severe diabetes, were
156 younger at diabetes diagnosis, and had diabetes of longer duration. To the best of our knowledge,
157 this is the first report documenting an independent association between diabetes mellitus and
158 UL. Indeed it is reasonable to expect such an effect of diabetes mellitus on UL formation.
159 Effects of diabetes mellitus on progression of atherosclerosis has been shown by the
160 demonstration of increased carotid artery intima-media thickness^{27,28}. Diabetes mellitus is
161 known to promote negative remodeling in the arterial wall and impairs compensatory arterial
162 enlargement during the course of the atherosclerotic process^{29,30}. Hyperinsulinemia is a good
163 candidate for UL formation by means of myometrial smooth muscle cell proliferation and/or
164 increasing circulating levels of ovarian hormones. Insulin resistance and hyperinsulinemia
165 have been proposed as possible mechanisms underlying pathophysiologic pathways
166 connecting obesity, diabetes, hypertension, and hyperlipidemia, eventually leading to
167 atherosclerosis³¹. Additionally, insulin has been shown to promote cell mitosis³², to promote
168 vascular smooth muscle proliferation³³, and, in particular, to stimulate the growth of UL cells

169 in tissue culture³⁴. Insulin may have also a specific gonadotropic function, stimulating ovarian
170 secretion via insulin receptors or receptors for insulin-like growth factors³⁵.

171 On the contrary, of previous literatures in which smoking has been reported as a
172 negative risk factor, we have found that smoking is positively and independently associated
173 with UL formation. Smoking has been reported to reduce the risk of UL in several
174 studies^{1,8,36,37}. No statistically significant associations have been observed between cigarette
175 smoking variables and UL risk. On the other hand smoking for more than 19 years is
176 associated with a 40 percent decreased risk of UL¹⁸. Although smoking is considered to be
177 associated with an estrogen-deficient state³⁸ which is supposed to be underlying reason of less
178 frequent UL in smokers in published literature, smoking is one of the major risk factor for
179 atherosclerosis. A common key element of atherosclerosis and UL is smooth muscle cell
180 proliferation. Recent epidemiological studies have shown that smoking is a significant and
181 independent risk factor for cardiovascular disease³⁹, and peripheral vascular disease⁴⁰.
182 Nicotine, a major constituent of tobacco is known to be directly involved in smooth muscle
183 cell proliferation⁴¹. UL has a monoclonal origin⁴², which has also been postulated for the
184 atheromatous plaque⁴³; cells from both conditions behave identically in culture⁴⁴. In terms of
185 smooth muscle cell proliferation, it is reasonable to expect a positive association with
186 smoking and UL.

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

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Table I. 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

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366 Table II. 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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