Creatine kinase and blood pressure: Clinical and therapeutic implications
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High blood pressure in women with uterine fibroids

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Submitted
Abstract

Background Women are at greater risk of premature cardiovascular death than men, with hypertension as a main risk factor. In search for female-specific risk factors, we assessed the independent association between uterine fibroids and hypertension.

Method In a hospital-based setting, we collected data on blood pressure in black and white patients admitted for surgery for uterine fibroids compared with women with other gynaecological surgery and population controls. Main reasons for exclusion were lack of blood pressure data and malignancy. We used multivariable binary logistic regression analysis to assess whether women with uterine fibroids were more likely to have high blood pressure, adjusted for age, body mass index and ethnicity.

Results We included 241 women with uterine fibroids (126 black), 308 women who underwent surgery for other gynaecological reasons (37 black), and 606 population controls (360 black), with a mean age of 43.4 (SD6.6), 41.3 (11.2), and 45.0 (6.6) y respectively, and mean BMI of 27.4 (5.3), 25.5 (5.4), and 28.0 (5.6) kg/m². High blood pressure was found in 43.6, 28.6, and 24.3% of the women with fibroids, other surgery, and population controls respectively. Women with fibroids were more likely to have high blood pressure after adjustment for age, BMI, and ethnicity with an odds ratio of 2.7 (95% CI, 1.9 to 3.9).

Discussion High blood pressure occurs more frequently in women with symptomatic uterine fibroids than in women with other gynaecological surgery and population controls, independent of age, BMI and ethnicity. Further research should establish whether this association is related to “growth prone” factors, and whether women with fibroids should be counselled for cardiovascular disease.
INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death for women, and more women than men die of heart disease each year.\(^1\) Importantly, women are less likely than men to receive aggressive diagnosis and treatment of cardiovascular disease, and nearly two-thirds of women who die of cardiovascular disease suddenly were not aware of her condition.\(^2\),\(^3\) Therefore, there is a need for strategies to fill the gaps in cardiovascular health care and health outcomes that exist between men and women.\(^4\)

Hypertension is a major risk factor for cardiovascular morbidity and mortality in women.\(^5\) The prevalence rate of hypertension equals that of men with more than 25% of women worldwide affected.\(^6\),\(^7\) Therefore, detecting and treating hypertension is a main measure to prevent premature cardiovascular death in this population subgroup. In search for sex-specific risk factors for cardiovascular disease, we assessed the occurrence of hypertension in women with uterine fibroids.

METHODS

Study design and population
Research procedures were approved and exempted from informed consent by our local institutional review board. In this retrospective analysis, we enrolled black and white women, age 18 to 60 y, who underwent surgery for symptomatic uterine fibroids at the department of Gynaecology in the Academic Medical Center, Amsterdam, the Netherlands, from January 2008 to December 2011. We compared this group of women with women who underwent gynaecological surgery for other reasons and population controls. Population controls were 606 self defined black and white women selected from participants in the “Surinamese in the Netherlands: Study on EThnicity and health” (SUNSET) Study: a stratified random population sample of 3000 noninstitutionalized persons (1000 white European and 2000 Surinamese-Dutch persons), aged 35 to 60 y, living in Amsterdam. The methods of this study have been described in detail elsewhere.\(^8\) We excluded women without blood pressure data, and women with a previous diagnosis of a malignant (gynaecological) tumor.

Data retrieval and analysis
We collected data on ethnicity, date of birth, height, weight, medical history, use of (anti-hypertensive) medication, and blood pressure as measured during pre-assessment for
surgery. Included women were contacted by telephone to verify self identified ethnicity. Blood pressure in women with uterine fibroids and surgical controls was measured once by a nurse at the outpatient clinic during pre-assessment with a Datascope Accutor Plus monitor. Blood pressure in the population controls was measured with an oscillometric automated digital BP device (Omron M4 oscillometric device: Omron Healthcare Europe BV, Hoofddorp, the Netherlands), with the mean of two readings used in the analyses. High blood pressure was defined as systolic pressure ≥140, or diastolic pressure ≥90 mm Hg, or receiving antihypertensive drugs. Body mass index (BMI) was calculated as weight (kg) divided by the height (rounded to the nearest centimeter) squared.

**Statistical analysis**

The primary outcome was the odds ratio of the occurrence of high blood pressure in women undergoing surgery for symptomatic uterine fibroids compared to women who underwent gynecological surgery for other reasons and population controls, after adjustment for age, BMI, and ethnicity. Secondary outcomes were differences in the occurrence of high blood pressure in women who underwent total uterine extirpation versus fibroid enucleation, as a surrogate measure of the severity of the condition; the occurrence of high blood pressure in women with fibroids compared to controls in different age categories (<40 versus ≥40 y); body weight categories (BMI ≤30 versus BMI >30 kg/m²), and black versus white women.

Sample size calculations for the primary outcome were based on a previous study comparing hypertension prevalence in women undergoing hysterectomy for uterine fibroids with hysterectomy for other reasons. For a multivariable logistic regression analysis with three other predictors, we calculated that 167 women were needed to enter the study (alpha 0.05, power 80%).

Crude differences in hypertension prevalence between groups were performed using the Chi-squared test. We used binary logistic regression analysis to assess whether women with uterine fibroids were more likely to have hypertension, adjusted for age, BMI, and ethnicity. A one-tailed $p$ value of 0.05 or less was considered statistically significant. Data were analyzed with SPSS statistical software package for Windows, version 19.0 (SPSS Inc., Chicago, IL, U.S.A.). Data in squared brackets are standard deviations unless stated otherwise.
RESULTS

We included 241 women with uterine fibroids, 308 women who underwent surgery for other gynaecological reasons, and the 606 population controls. The characteristics of the included women are shown in Table 1. Notably, women admitted for fibroids were more often black compared to women admitted for other surgery, respectively 52.3 vs. 12.0%. The population sample was stratified for ethnicity and 59.4% of the included women were black.

Table 1. Patient characteristics.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Surgery for uterine fibroids</th>
<th>Other gynaecological surgery</th>
<th>Population controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of women</td>
<td>241</td>
<td>308</td>
<td>606</td>
</tr>
<tr>
<td>Age (years)*</td>
<td>43.4 ± 6.6</td>
<td>41.3 ± 11.2</td>
<td>45.0 ± 6.6</td>
</tr>
<tr>
<td>BMI (kg/m²)*</td>
<td>27.4 ± 5.3</td>
<td>25.5 ± 5.4</td>
<td>28.0 ± 5.6</td>
</tr>
<tr>
<td>Obesity (%)</td>
<td>27.0</td>
<td>15.6</td>
<td>31.5</td>
</tr>
<tr>
<td>Black ethnicity (%)</td>
<td>52.3</td>
<td>33.8</td>
<td>40.6</td>
</tr>
<tr>
<td>SBP (mm Hg)*</td>
<td>133.2 ± 18.3</td>
<td>126.6 ± 15.7</td>
<td>122.9 ± 21.1</td>
</tr>
<tr>
<td>DBP (mm Hg)*</td>
<td>81.4 ± 11.0</td>
<td>75.9 ± 10.8</td>
<td>79.9 ± 12.1</td>
</tr>
<tr>
<td>High blood pressure (%)</td>
<td>43.6</td>
<td>28.6</td>
<td>24.3</td>
</tr>
</tbody>
</table>

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; High blood pressure is defined as systolic pressure ≥140, or diastolic pressure ≥90 mm Hg, or receiving antihypertensive drugs. *Values are mean ± SD.

The prevalence of high blood pressure was significantly higher in women with fibroids compared to women admitted for other surgery and population controls, respectively 43.6%, 28.6% and 24.3% (p<0.001 for comparisons between women with fibroids and controls), with respectively 38.5, 51.1, and 22.4% of women with high blood pressure using antihypertensive drugs (p=0.006 for the difference between women with fibroids and population controls, p=0.078 for the difference between fibroids and other surgery; p<0.001 for the difference between women admitted for other surgery and population controls) (Figure 1). In women who underwent a total uterine extirpation for fibroids, high blood pressure was more common compared to women who underwent fibroid enucleation, respectively 52.7 and 35.7% (p<0.001). The occurrence of high blood pressure was age-dependent as expected (Figure 2, panel A) and higher in obese and
black women (Figure 2, panel B and C). For white women, high blood pressure prevalence was 42.1% in women with and 21.4% in women without fibroids ($p<0.001$). For black women, this was 45.2 and 31.0% in women with and without fibroids respectively ($p=0.003$) (Figure 2).

In univariable logistic regression analysis, the odds ratio for having high blood pressure with surgery for uterine fibroids was 2.23 (95% CI, 1.66 to 3.00). After adjustment for age, BMI, and ethnicity in multivariable logistic regression analysis undergoing surgery for fibroids was the main predictor of having high blood pressure, with an odds ratio of 2.71 (95% CI, 1.89 to 3.89) (Table 2).

![Figure 1. Prevalence of high blood pressure and antihypertensive treatment in women with fibroids versus controls.](image)

Vertical bars represent the prevalence of high blood pressure (systolic/diastolic blood pressure ≥140/90 mm Hg or antihypertensive treatment) and the percentage of those subjects on antihypertensive treatment in women with fibroids, other gynecological surgery, and population controls. The prevalence of high blood pressure is significantly higher in women with fibroids compared to women admitted for other surgery and population controls. The percentage of women with high blood pressure using antihypertensive drugs was higher in women admitted for surgery compared to population controls. *$p<0.001$ compared to population controls and women admitted for other surgery; **$p<0.001$ and ***$p=0.006$ compared to population controls.
Figure 2. Prevalence of high blood pressure in women with fibroids versus controls divided in age groups (A), non obese and obese (B), and white and black ethnicity (C).

Vertical bars represent the prevalence of high blood pressure in women with and without fibroids in different age categories (panel A), non obese (BMI <30 kg/m$^2$) and obese (BMI ≥30 kg/m$^2$) (panel B), and for white and black ethnicity (panel C). *p<0.01, **p<0.001 versus women without fibroids.

Table 2. Odds ratios for hypertension.

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Odds ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibroids</td>
<td>2.71 (1.89 to 3.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Black ethnicity</td>
<td>1.18 (1.05-1.32)</td>
<td>0.004</td>
</tr>
<tr>
<td>Age*</td>
<td>1.10 (1.08-1.13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI*</td>
<td>1.10 (1.07-1.13)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

BMI, body mass index. * for increasing age and BMI.

**DISCUSSION**

The main finding of this study is that women admitted for surgery for fibroids are 2.7 times more likely to have high blood pressure compared to women admitted for other gynaecological surgery and population controls, independent of age, BMI, and ethnicity.

Although uterine leiomyomata are the most common pelvic benign tumors, little is known about cardiovascular health implications of this condition. In the recent largest rapport on the prevalence, symptoms, and management of uterine fibroids including more than 20,000 women, data on the prevalence of hypertension or cardiovascular disease were not reported. In addition, although current guidelines
for prevention of CVD in women emphasize that conditions associated with increased CVD risk should be recognized and that those women should be screened for other risk factors, uterine fibroids as a risk factor for hypertension is not mentioned. This is in spite of the fact that there are numerous anecdotal, retrospective, cross-sectional, case-control, and prospective cohort studies where this association is shown, including a greater occurrence in black women.

Several hypotheses for the association between hypertension and uterine fibroids have been forwarded, including surveillance bias, a common association with obesity, sex steroids, and hormone replacement therapy. Furthermore, it was proposed that the uterus with fibroids might affect the renin angiotensin system, due to extrarenal excretion of angiotensin forming enzymes or increased renal renin excretion, which is thought to be due to urethral obstruction by the enlarged uterus or concurrent leiomyomata. However, evidence supporting this theory is lacking.

The most common hypothesis forwarded is that high blood pressure and fibroids share a common “growth prone” pathophysiology, of cardiac, smooth vascular and smooth uterine tissue. Several hormones (angiotensin II, insulin, ovarian steroids) and growth factors (transforming growth factor β1, epidermal growth factor, insulin like growth factor), implicated in proliferation and remodeling of smooth muscle, were postulated to link uterine fibroids with hypertension. The enzyme creatine kinase is another potential candidate. Creatine kinase, in particular the B isoenzyme is known to provide ATP to neoplasms. In addition, CK has been causally implicated in hypertension. Therefore, we propose that the ATP buffering CK system might be a common intracellular pathway of cellular growth responses in hypertension and uterine fibroids. The enzyme catalyzes the reversible transfer of a high-energy phosphate group from phosphocreatine to ADP, creating ATP. CK is tightly bound near ATPases involved in ion transport, smooth, cardiac, and skeletal muscle contractility and growth, where it serves to rapidly provide ATP for ATPases. As the enzyme directly provides ATP for pressor responses as well as for muscle hypertrophy, the high creatine kinase state might enhance vascular contractility as well as growth responses, promoting hypertension. Interestingly, relatively high CK activity is found in uterine fibroid tissue compared to adjacent myometrium. Clearly, more studies are needed in this field.

The main strength of this study is that we present a large sample of women of European and African ancestry and include surgical and population controls. In
addition, we showed that the association between hypertension and uterine fibroids is independent of common risk factors.

We acknowledge that this study has several limitations. First the retrospective design of the study includes a risk for selection and information bias, and temporal relationships cannot be assessed. Furthermore, we used single blood pressure measurements to define high blood pressure. Possibly, blood pressure levels were increased due to stress regarding the upcoming surgical procedure. This would have led to an overestimation of the prevalence of hypertension in women with fibroids. However, we also found a significantly prevalence of hypertension in women with fibroids compared to surgical controls, with equal blood pressure readings. Finally, the prevalence of uterine fibroids in the population sample is not known. However, if the association between blood pressure and fibroids is also present in the population, this would probably have led to an underestimation of the difference in hypertension prevalence between women with and without fibroids.

In summary, women with fibroids are around three times more likely to have hypertension compare to surgical and population controls, independent of age, BMI, and ethnicity. As hypertension and cardiovascular disease pose a considerable threat to women worldwide, increased physician and patient awareness on hypertension and increased risk for cardiovascular disease in women with fibroids is needed.
REFERENCES


