Original Paper

Systemic Hypertension Among Women With Uterine Leiomyomata: Potential Final Common Pathways of Target End-Organ Remodeling

Marc A. Silver, MD;[1,2] Rashmi Raghuvir, MD;[2] Bohdan Fedirko, MD;[3] Denise Elser, MD[4]

The uterus and the heart share a common structure and may remodel in a similar fashion, albeit temporally distinct. The authors investigated the prevalence of systemic hypertension in women with uterine leiomyomata (fibroids) and compared the prevalence in women undergoing hysterectomy for other reasons as well as in age-matched women from the National Health and Nutrition Examination Survey III (NHANES III). A total of 584 women, 205 with leiomyomata in 1999 (group A) and 379 who underwent hysterectomy for a variety of reasons in 2000 (group B) at Advocate Christ Medical Center were included. Presence of leiomyomata was confirmed by pathology. Hypertension was defined as blood pressure ≥140/90 mm Hg or history of hypertension with or without medication use. The prevalence of hypertension in group A and B patients with leiomyomata compared with NHANES III overall was 48.6% vs. 24% (p<0.001), in African Americans 55.5% vs. 32.4% (p<0.001), and in Caucasians 51.1% vs. 23.3% (p<0.001). Leiomyomata were more frequent among hypertensive than normotensive women (57% vs. 27%). Caucasian and African-American women with leiomyomata were significantly younger and more likely to use hormone replacement therapy than others. Thus there appears to be an association between leiomyomata and hypertension, which needs to be explored in future prospective trials. (J Clin Hypertens. 2005;7:664–668) ©2005 Le Jacq Ltd.

From the Heart Failure Institute;[1] the Departments of Medicine[2] and Obstetrics and Gynecology;[3] and the Cardiology Fellowship Program,[4] Advocate Christ Medical Center, Oak Lawn, IL
Address for correspondence:
Marc A. Silver, MD, Clinical Professor of Medicine, University of Illinois, Chairman, Department of Medicine, Director, Heart Failure Institute, Advocate Christ Medical Center, 4440 West 95th Street, Suite 319 South, Oak Lawn, IL 60453
E-mail: marc.silver@advocatehealth.com
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Hypertension is a major public health problem in the United Sates and worldwide, being the second most common reason for office visits and prescriptions. More than 50 million Americans suffer from hypertension, and two million people are diagnosed with it each year.[1] Hypertension continues to be a major cause of morbidity and mortality. According to the National Health and Nutrition Examination Survey III (NHANES III), age-adjusted prevalence of hypertension between 1988 and 1991 was 32.4% in the non-Hispanic black population and 23.3% in the non-Hispanic white and Mexican-American population. Hypertension occurs in over half of all patients older than 65 years.[2] Since the development of systemic hypertension and left ventricular hypertrophy (LVH) increases the risk of cardiovascular morbidity and mortality, attempts to define a patient population with early systemic hypertension or even those at risk for systemic hypertension seem worthwhile.

Leiomyomata, or uterine fibroids, are one of the most frequent gynecologic diagnoses. Thirty percent of all hysterectomies done in the United States are for leiomyomata and, although most patients are asymptomatic, one in every four women will have uterine leiomyomata that may

need to be treated.[3] Earlier studies showed a higher prevalence of hypertension in women who had undergone hysterectomies for leiomyomata compared with those who had undergone hysterectomies for other reasons.[4]

The role of the complex renin–angiotensin system is an important one not only in terms of the cardiovascular, renal, and reproductive systems, but also in its contribution to the prevalence and progression of hypertension, vascular diseases, cardiac hypertrophy, heart failure, diabetic renal disease, and possibly leiomyomata.

BACKGROUND AND RATIONALE

The uterus and the heart are organs that are somewhat similar in structure, contractile function, and remodeling properties due to hypertrophy and excess collagen matrix growth. There appear to be certain similarities when considering the pathogenesis of hypertension, uterine leiomyomata, and cardiac remodeling. The circulating renin–angiotensin system plays a role in LVH and fibrosis and is also implicated in the pathogenesis of hypertension.[5–8]

Angiotensin II (AT-II) has a proliferative action in that it stimulates the hypertrophy of cardiac and vascular smooth muscle by inducing certain proto-oncogenes and autocrine growth factors such as platelet-derived growth factor A, transforming growth factor β1, and basic fibroblast growth factor.[6,7] Local expression of some 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.[9,10] AT-II receptors have been found in various tissues, including the uterine myometrium and in vascular smooth muscle cells.[11] These are of two receptor types, namely AT_1 and AT_2. AT-II–mediated stimulation of the AT_1 receptor in vascular smooth muscle induces proliferation and hypertrophy.[12] On the other hand, the expression and activation of the AT_2 receptor results in an antiproliferative effect.[13]

The effects of AT-II are influenced by estrogen and progesterone.[14,15] During pregnancy and oral contraceptive use, there is an up-regulation of the AT_1 receptor, thus mediating hypertrophy and hyperplasia of the uterus. On the other hand, there is a down-regulation of the antiproliferative AT_2 receptors within uterine leiomyomata, thus allowing for the unopposed action of AT-II. This facilitates the growth of the leiomyomata.[9,16–18] Similar changes in the vasculature favor the development of systemic hypertension.

The effects of AT-II mediated through angiotensin receptors cause vasoconstriction, cell growth, and endothelial dysfunction and are associated with progressive fibrosis.[6] AT-II thus plays a major role in the pathogenesis of hypertension and may have a role in the development of uterine leiomyomata. Thus, there appears to be a final common mediator in the pathogenesis of these conditions. It has been postulated that this mediator might be AT-II, thus accounting for the high prevalence of hypertension in a population with uterine leiomyomata. We sought to verify this association.

MATERIALS AND METHODS

The subjects were identified from the medical records of Advocate Christ Medical Center. A total of 584 women were included: 205 women who presented consecutively with leiomyomata in 1999 (group A) and 379 women who underwent hysterectomy for a variety of reasons in 2000 (group B). To better evaluate possible racial variance and contribution to this observation, only African-American and Caucasian women were included in this study.

Preoperative information on indications for the procedure, current use of hormone replacement therapy or other medication, body mass, and blood pressure (BP) was obtained from medical records. The presence of leiomyomata was confirmed from the pathology report. Women were classified as hypertensive if they were currently taking antihypertensive medication, had a history of hypertension without current medication, or had a preoperatively measured systolic BP ≥140 mm Hg and/or diastolic BP ≥90 mm Hg.

Reasons for hysterectomy in group B included leiomyomata (intramural, subserosal, or submucosal); excessive menstruation; uterine and uterovaginal prolapse; benign neoplasms of the ovaries including corpus luteal cysts; ovarian cyst necrosis; malignant neoplasms of the ovaries, fallopian tubes, or corpus uterus; endometriosis; endometrial hyperplasia; dysplasia; cancer of the cervix; or cervicitis.

The chi-square test, independent *t* test, and the Kolmogorov-Smirnov test were used for statistical analyses. Statistical analyses were first performed to determine whether there were any differences between the 1999 and the 2000 leiomyoma groups. No statistical differences were found between the two groups; therefore the two groups were combined for the analyses.

Data were analyzed according to hypertension, age, race, weight, current hormone replacement therapy use, use of other medications, and history of smoking. The results obtained were then compared as follows: the prevalence of hypertension

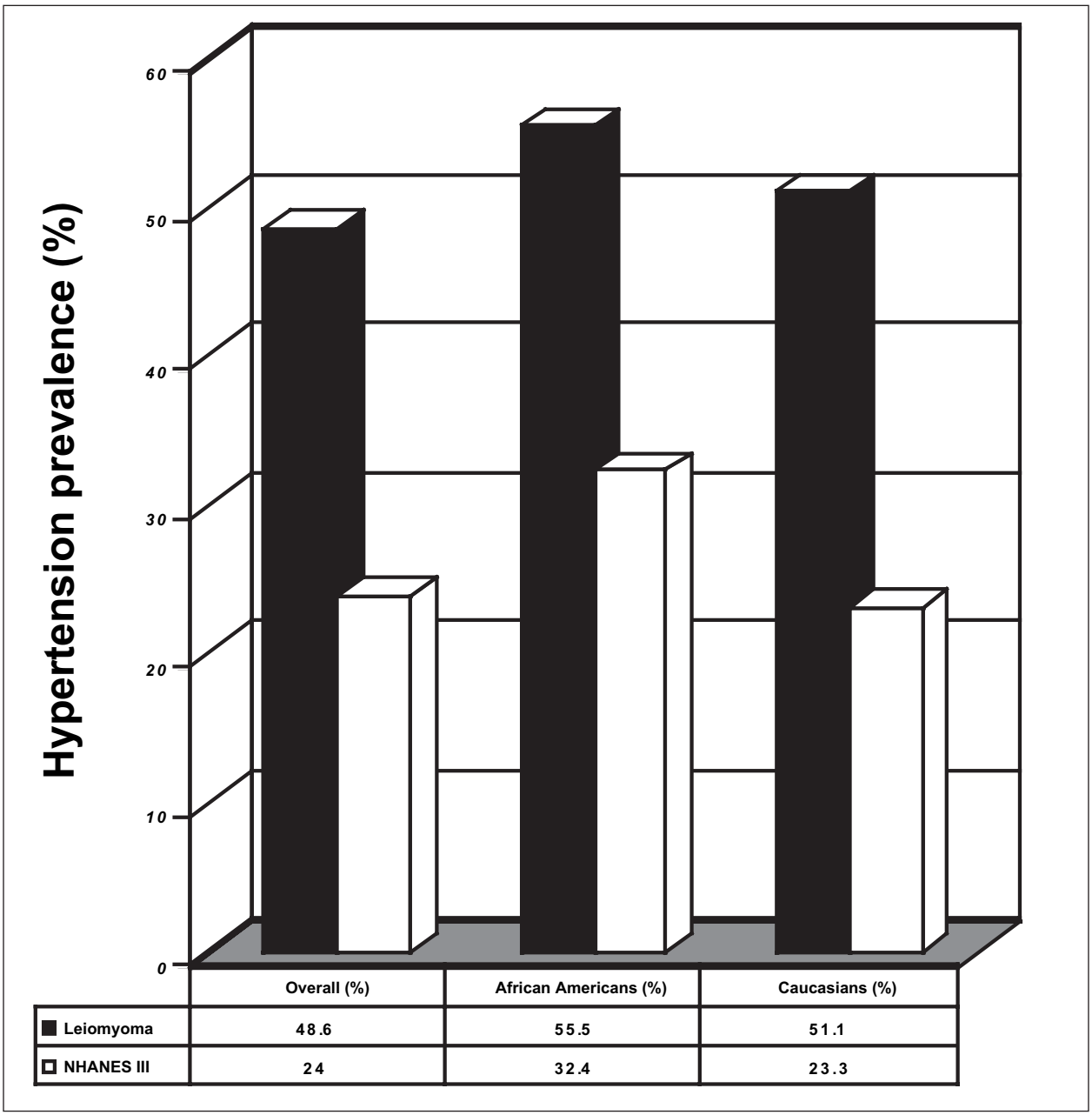

Figure. Hypertension prevalence in women with leiomyomata vs. National Health and Nutrition Examiniation Survey III (NHANES III) (p<*0.001, all groups)*

among patients with leiomyomata in groups A and B were compared with the NHANES III data; the prevalence of hypertension in patients with leiomyomata in groups A and B was compared with that in patients who had hysterectomies for other reasons in group B (i.e., patients with leiomyomata vs. patients without leiomyomata).

Hispanic and other minority groups were eliminated from all analyses due to the small number of each. Therefore, this study only analyzes Caucasian and African-American women. Three age groups (30–39, 40–49, and 50 years or older) were considered. There were limited patients under the age of 30 years.

RESULTS

Statistical analyses revealed that in this series of nonrandomized patients, African Americans were significantly (7.09 times) more likely than Caucasian women to have leiomyomata (chi-square $p<0.0001$)

When looking at patients with leiomyomata, African Americans with leiomyomata in the 30–39-year age group were found to be 3.78 times more

likely than Caucasians with leiomyomata in this age group to have hypertension. The results were statistically significant (chi-square $p<0.019$). These findings may, however, reflect the fact that African Americans develop hypertension at a younger age.

The combined data for the two groups are as follows (Figure). The prevalence of hypertension in all women with leiomyomata compared with NHANES III data was 48.6% vs. 24%, respectively ($p<0.001$). In African-American women it was 55.5% vs. 32.4% ($p<0.001$), and among Caucasian women it was 51.1% vs. 23.3% ($p<0.001$). Uterine leiomyomata were also more frequent among hypertensive than normotensive women (57% vs. 27%). Caucasian and African-American women with leiomyomata were younger and more likely to use hormone replacement therapy than other women.

The study population included 22% African-American women and 78% Caucasian women. The prevalence of hypertension in African-American patients with leiomyomata compared with those without leiomyomata was 55.5% vs. 30%, and among Caucasian patients, 51.1% vs. 51.35%.

DISCUSSION

Due to the public health importance of the early detection and treatment of hypertension, the search continues for biomarkers or host or environmental factors that may allow for earlier surveillance and detection of hypertension to attenuate its heart and vascular remodeling effects. We suggest that the presence of uterine leiomyomata in women may be one such marker that, along with BP measurements, may provide a clue to organ changes associated with hypertension.

We similarly postulate that the uterus and the heart are organs that are similar in structure and contractile function and capable of undergoing hypertrophy and remodeling. It has been well established that the renin–angiotensin system plays a crucial role in the development and maintenance of LVH and fibrosis and is similarly involved in the pathologic processes in hypertension. It appears that AT-II, under the influence of estrogen and progesterone, may be implicated in the pathogenesis of uterine leiomyomata. AT-II may serve as a catalyst for the development of these two conditions, and the appearance of leiomyomata might thus be a forerunner of essential hypertension in women.

The study is limited by the fact that it is a retrospective series and analyzes only Caucasian and African-American women; however, it draws attention to a possibly important potential association between uterine leiomyomata and hypertension. Further prospective studies are needed. Next steps include determinations of AT-II levels in similar populations of women to attempt to elucidate the link between uterine and heart remodeling. A syndrome of clinically related findings (Silver syndrome) including a history of hysterectomy for uterine leiomyomata, systemic hypertension, and microvascular angina associated with microvascular remodeling has recently been noted by our group and presented during the Hyde Park sessions at the Heart Failure Society of America.[19] Typically, these women have significant LVH. This syndrome has been observed in African American, Caucasian, and Hispanic women of various ages.

We believe that the data presented highlight the natural history of target organ remodeling and emphasize the need for higher levels of awareness of the role of systemic hypertension as a systemic disease process.

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REFERENCES

1 Hajjar I, Kotchen TA. Trends in prevalence, awareness, treatment, and control of hypertension in the United States, 1988–2000. *JAMA*. 2003;290:199–206.
2 Burt VL, Whelton P, Roccella EJ, et al. Prevalence of hypertension in the US adult population. Results from the Third National Health and Nutrition Examination Survey, 1988–1991. *Hypertension*. 1995;25:305–313.
3 *Management of Uterine Fibroids: Summary*. Rockville, MD: Agency for Healthcare Research and Quality, US Dept of Health and Human Services; 2001. Evidence Report/ Technology Assessment Number 34. AHRQ Publication No. 01E051.
4 Luoto R, Rutanen EM, Auvinen A. Fibroids and hypertension. A cross sectional study of women undergoing hysterectomy. *J Reprod Med*. 2001;46:359–364.
5 Kawano H, Do YS, Kawano Y, et al. Angiotensin II has multiple profibrotic effects in human cardiac fibrosis. *Circulation*. 2000;101:1130–1137.
6 Itoh H, Mukoyama M, Pratt RE, et al. Multiple autocrine growth factors modulate vascular smooth muscle cell growth response to angiotensin II. *J Clin Invest*. 1993;91:2268–2274.
7 Bishop JE, Kiernan LA, Montgomery HE, et al. Raised blood pressure, not renin angiotensin systems, causes cardiac fibrosis in TGR m(Ren2)27 rats. *Cardiovasc Res*. 2000;47:57–67.
8 Everett HS, Scott RB. Possible etiologic role of gynecological lesions in production of hypertension. *Am J Obstet Gynecol*. 1942;44:1010–1025.
9 Brandon DD, Bethea CL, Strawn EY, et al. Progesterone receptor messenger ribonucleic acid and protein are overexpressed in human uterine leiomyomas. *Am J Obstet Gynecol*. 1993;169:78–85.
10 Dou Q, Zhao Y, Tarnuzzer RW, et al. Suppression of transforming growth factor-beta (TGF beta) and TGF beta receptor messenger ribonucleic acid and protein expression

in leiomyomata in women receiving gonadotropin-releasing hormone agonist therapy. *J Clin Endocrinol Metab*. 1996;81:3222–3230.
11 Baker KM, Booz GW, Dostal DE, et al. Cardiac actions of angiotensin II: role of intracardiac renin angiotensin system. *Annu Rev Physiol.* 1992;54:227–241.
12 Daemen MJ, Lombardi DM, Bosman FT, et al. Angiotensin II induces smooth muscle proliferation in the normal and injured rat arterial wall. *Circ Res*. 1991;68:450–456.
13 Nakajima M, Hutchinson HG, Fujinaga M, et al. The angiotensin II type 2 (AT2) receptor antagonizes the growth effects of the AT1 receptor: gain-of-function study using gene transfer. *Proc Natl Acad Sci U S A*. 1995;92:10663–10667.
14 Raij L, Johnston B. Estrogen deficiency promotes hypersensitivity- the hypertensinogenic effect of angiotensin II. *Am J Hypertens*. 2000;13:S29.
15 Ito M, Nakamura T, Yoshimura T, et al. The blood pressure response to infusions of angiotensin II during normal pregnancy: relation to plasma angiotensin II concentration, serum progesterone level, and mean platelet volume. *Am J Obstet Gynecol*. 1992;166:1249–1253.
16 de Gasparo M, Whitebread S, Kalenga MK, et al. Down regulation of the angiotensin II receptor subtype AT2 in human myometrium during pregnancy. *Regul Pept*. 1994;53:39–45.
17 Matsumoto T, Sagawa N, Mukoyama M, et al. Type 2 angiotensin II receptor is expressed in human myometrium and uterine leiomyoma and is down regulated during pregnancy. *J Clin Endocrinol Metab*. 1996;81:4366–4371.
18 Schirar A, Capponi A, Catt KJ. Regulation of uterine angiotensin II receptors by estrogen and progesterone. *Endocrinology.* 1980;106:5–12.
19 Silver MA. Hearts and uterii. Abstract presented at: 2005 Hyde Park Session, Heart Failure Society of America 9th Annual Scientific Meeting; September 20, 2005; Boca Raton, FL.