ISSN: 2634 - 1255

Journal of Gynecology Research Reviews & Reports

SCIENTIFIC Research and Community

Research Article

Open Access

Comparative Plasma Levels of Angiotensin II in Women with or without Uterine Fibroid in Lagos State University Teaching Hospital, Ikeja, Lagos, Nigeria

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ABSTRACT

Background: Uterine fibroid is the most common tumour in women reproductive age group Recently uterine fibroids have been noticed to be more common in patients with hypertension, another disease with a predilection for the black race. The study compares the serum levels of angiotensin II in women with uterine fibroids and women without uterine fibroids.

Methods/Designs: The study was a prospective case-controlled study involving ninety consecutive women with a confirmed diagnosis of uterine fibroids and ninety consecutive women with intact uterus with no sonological diagnosis of uterine fibroids matched for age, parity and body mass index. A structured interviewer-administered questionnaire was completed for each subject, who also had their blood pressure checked in the clinic and 5ml of venous blood drawn for angiotensin 2 assay. The uterine size was measured in pregnancy weeks. The data obtained were processed and analyzed using Statistical Package for Social Sciences, (SPSS) version 20.

Results: The mean serum level of angiotensin II in women with uterine fibroids was significantly higher than that in women without uterine fibroids, (0.71±0.07ng/ml vs. 0.23±0.07ng/ml), p <0.001. The mean systolic blood pressure was significantly higher in respondents with uterine fibroids (122.99±16.01 vs. 112.92±13.22mmhg), p<0.001. Women with uterine fibroids were about six times more likely to have hypertension than women without fibroids, p= 0.01. Conclusion: Uterine fibroids and hypertension are associated with higher levels of angiotensin II, suggesting a possible important aetiological role in both by angiotensin II.

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Received: March 09, 2022; **Accepted:** March 14, 2022; **Published:** March 24, 2022

Keywords: Angiotensin II, Fibroid, Women

Introduction

Uterine fibroid which is also referred to as ''leiomyoma is the most common benign tumour in women of reproductive age group [1]. It is estimated that 20 – 25% of reproductive-age women have clinically symptomatic fibroids [1,2]. It is the commonest cause of gynaecological admission and hysterectomy in the USA [2]. In Nigeria, uterine fibroids are responsible for 3 to 7.8% of new gynaecological cases, 3 to 13.6% of gynaecological admissions, 26.2% of major gynaecological surgery and 68.1% of hysterectomies [1,3].

Despite its public health importance, the aetiology of uterine fibroid is poorly understood. Risk factors include age especially women within the age group of 30-44 years, African race, obesity, diet rich in beef and ham, excessive radiation, family history, early age at menarche, infertility and alcohol consumption [1,2,4].

Uterine fibroids are 2-3 times more common in blacks showing a propensity for race and ethnicity [2,5]. As many as 50% of black women and 35 % of Caucasians will have leiomyomata by their fifth decade [2]. Fibroids in blacks are larger and are more symptomatic making them seven times more at risk for myomectomy and twice more likely to undergo hysterectomy than their white counterparts [4,5].

In view of the genetic predisposition, black have also been known to have a higher propensity for hypertension with a higher incidence of renal and cardiovascular complications and a poor response to treatment [6].

Similarly, several studies have previously shown a relationship between fibroid and hypertension through diverse pathways [6,7,8].One of such is the possibility that the association may also be related to the effect of angiotensin II [9,10,11].

Angiotensin II is the most active hormone in the rennin-angiotensin system (RAS) [10]. Its action, apart from the classic control of blood pressure, has been linked to cell growth including cancer formation, tissue remodelling, inflammation, angiogenesis and apoptosis [12]. Excessive activation of the RAS pathway is thought to play a key

role in the development of essential hypertension [11].

Angiotensin II is an octapeptide hormone derived from angiotensin I, a decapeptide through the action of angiotensin-converting enzyme (ACE) which cleaves two amino acids from the carboxyl terminus of angiotensin I [6,12]. This acts on angiotensin Iand 11 receptors (ATRI and ATRII) which are both the heart and uterus [12].

In the past, several studies linked the association between hypertension and uterine fibroids on the effect of obstruction on the kidneys due to pressure symptoms from large fibroids, but this reverse-causality interpretation has been questioned [12]. These angiotensin II receptors are present in various tissues including the uterus and vascular smooth muscles. And stimulation of these ATR1 receptors and epidermal growth factor receptor by the ligand Ang-II induces fibroid cell proliferation [11-13].

Angiotensin receptor blockers (ARB) such as telmisartan and losartan have also been shown to inhibit both angiotensins 11-induced leiomyoma cell growth in-vitro and in uterine leiomyoma [11,12]. Thus, potentiate the fact that angiotensin II plays a major role in the pathogenesis of both hypertension and uterine fibroid, and this may explain why the prevalence of hypertension is higher in women with uterine fibroid [11-14]. This proposed study, therefore, sets out to determine and compare the serum levels of angiotensin 11 in women with uterine fibroids with values in women without uterine fibroids using a prospective case-controlled study. It is also hoped that any relationship between uterine fibroid, hypertension and serum angiotensin 11 will be determined

Methodology

The study was conducted at the Obstetrics and Gynaecology Department of the Lagos State University Teaching Hospital (LASUTH), Ikeja, Lagos State. The study lasted for 6 months. A case-control study designed to determine the relationship between the angiotensin level and uterine fibroids in women attending gynaecology clinic in the department of Obstetrics and Gynaecology, Lagos State University Teaching Hospital (LASUTH) Ikeja, Lagos. Inclusion criteria are consenting patients with a confirmed diagnosis of uterine fibroid (cases) and patients without uterine fibroid (controls). Exclusion criteria are denial of consent, presence of other abdominal masses apart from uterine fibroids. Known patients with hypertension were not excluded from the study because one of the objectives of the study was to determine if hypertension is associated with uterine fibroids. However all medications especially ACE inhibitors, which have the potential to reduce angiotensin II levels were noted for the purpose of data analysis. Consecutive patients with a diagnosis of uterine fibroids confirmed by ultrasound, who consented to the study, were recruited as cases, while those with sonological evidence excluding uterine fibroid were recruited as controls.

Sample Size: The sample size for the study was calculated using the formula for case-controlled study [15].

$$N = \frac{\{z\alpha\sqrt{2pq} + z\beta(\sqrt{p_1q_1} + P_0q_0)}{(p_1-p_0)^2}$$

P_0=2.5 [16]

This was a case-control study, a total of 180 women participated in this study made up of 90 women with a current diagnosis of uterine fibroid as cases and 90 women with sonological evidence of intact uterus without uterine fibroid as control. The ages of the cases were matched with their control counterparts with a range of zero to two years, so as to remove the effect of age on hypertension. The parity and BMI of the cases were also as much as possible match with their control. Matching for parity was done using a range of zero to one while matching for BMI was done using a range of zero to 2kg/m^2.

Ethical Consideration

The study protocol was approved by the Health Research Ethics and Committee of the Lagos State University Teaching Hospital The participants were counseled on the research protocol in a language they understood. Questions and samples were collected from informed subjects who had given their written consent for inclusion in the study.

Data and Sample Collection

Data was collected from selected eligible participants using well-structured questionnaires administered by the investigator to obtain participants' personal information.

All the participants were also weighed and their heights were taken so as to determine the body mass index. The interviews were confidential with the participant well relaxed, their blood pressure were also measured in the clinic using American Heart Association criteria using a sphygmomanometer [17]. A total of two blood pressure measurements were taken at least one minute apart. The average of the two measurements was then taken as the patient's blood pressure. All the participants also had about 5ml of venous blood collected into a plain bottle by venepuncture from the ante-cubital fossa under aseptic conditions. These samples were used to determine the serum level of angiotensin II in all the participants. The uterine fibroid was confirmed using an ultrasound scan and the size of the fibroid was assessed in pregnancy weeks.

The angiotensin II assay kit used for this study was ab108796 Angiotensin II Human ELISA kit manufactured by Abcam United Kingdom [18].

The data obtained were entered and analyzed using Statistical Package for Social Sciences, version 20. Descriptive statistics such as mean, standard deviation, range and simple percentages were used. Odds ratios with 95% confidence intervals were also calculated where necessary. P-values less than 0.05 were considered statistically significant at a 95% confidence interval.

Results

A total of 180 women participated in this study. This was made up of 90 women with current diagnosis of uterine fibroid as cases and 90 women with sonological evidence of intact uterus without uterine fibroid as control. The mean age of the case group was 38.34±7.16 years while that of the control was 37.52±7.04 years. There was no statistical difference in the mean age of the two groups. Table 1 summarizes the socio demographic data of the two groups. There was no statistical difference in the socio demographic data except in the social classification. There were more respondents amongst cases who were in the middle and upper social class when compared to the control. This difference was statistically significant with p value of 0.023.

Thirteen (7.2%) of the total population were hypertensive, out of which eleven had uterine fibroids and two had no fibroids. Five (38.5%) of those with hypertension were not on medication, 5(38.5%) were on single therapy with calcium channel blockers, while the remaining 3(23%) were on combination therapy with diuretics and calcium channel blockers.

Table 1: Sociodemographic Characteristics of Studied Population

Variable	Case group n = 90 (%)	Control group n = 90 (%)	X^2	p
Age group(Years)				
20 - 29	11 (12.2)	12 (13.3)	0.583	0.900
30 – 39	40 (44.4)	44 (48.9)		
40 - 49	33 (36.7)	29 (32.2)		
≥50	6(6.7)	5 (5.6)		
Level of education				
Primary	4 (4.4)	9 (10)	5.126	0.077
Secondary	24 (26.7)	33 (36.7)		
Tertiary	62(68.9)	48(53.3)		
Marital status				
Single	25(27.8)	18(20)	3.740	0.291
Married	63(70)	72(80)		
Separated/widowed	2(2.2)	0(0)		
Occupation				
Skilled	42 (46.7)	35(38.9)	7.118	0.068
Semi skilled	38 (42.2)	49(54.4)		
Unskilled	5 (5.6)	0(0)		
Unemployed	5 (5.6)	6(6.7)		
Religion				
Christianity	74 (82.2)	73 (81.1)	0.037	0.847
Islam	16 (17.8)	17 (18.9)		
Social class				
Upper	4 (4.4)	2 (2.2)	7.511*	0.020
Middle	57 (63.4)	41 (45.6)		
Lower	29 (32.2)	47 (52.2)		
Parity				
Nulliparous	68 (75.6)	59 (65.6)	2.921	0.232
Multiparous	19 (21.1)	29 (32.2)		
Grandmulti	3 (3.3)	2 (2.2)		

* signifies Fisher exact test

Serum Levels of Angiotensin 11

Table 2 shows the distribution of serum angiotensin 2 in respondents with uterine fibroids (study group) and those without uterine fibroid (control). The mean angiotensin 2 level was 0.71ng/ml ± 0.069ng/ml. The serum levels range between 0.42ng/ml to 0.85ng/ml, with a median concentration of 0.73ng/ml and a modal concentration of 0.75ng/ml.

Table 2: Serum Angiotensin II levels in the Case and Control groups

Serum Angiotensin II levels (ng/ml)	Number in Study group N = 90 (%)	Number in control group N = 90 (%)
0.01 – 0.09	Nil (0.0)	5 (5.6)
0.10 – 0.19	Nil (0.0)	19 (21.1)
0.20 - 0.29	Nil (0.0)	52 (57.8)
0.30 – 0.39	Nil (0.0)	13 (14.4)
0.40 – 0.49	1 (1.1)	1 (1.1)
0.50 – 0.59	6 (6.7)	Nil (0.0)
0.60 – 0.69	8 (8.9)	Nil (0.0)
0.70 – 0.79	74 (82.2)	Nil (0.0)
0.80 – 0.89	1 (1.1)	Nil (0.0)
TOTAL	90 (100.0)	90 (100.0)

The mean angiotensin II level in the study group, 0.71±0.069 ng/ml is significantly higher than the mean angiotensin II level in the control group, 0.23±0.07 ng/ml (t=46.976, p<0.001). For the study group the levels range from 0.42 to 0.85ng/ml and for the control group from 0.06 to 0.41ng/ml.

The mean angiotensin 2 level in the control group was 0.23ng/ml ± 0.07ng/ml. The serum levels ranges between 0.06ng/ml to 0.41ng/ml, with a median concentration of 0.23ng/ml and a modal concentration of 0.21ng/ml. When the mean of the two groups were compared as shown in Table 3, the difference was statistically significant with $p < 0.001$.

Relationship between Studied Variables and Presence of Uterine Fibroids

Table 3 summarizes the relationship between the studied variables and the presence of uterine fibroids. Only consumption of vegetables and fruits, and presence of hypertension have statistically significant relationship to presence of uterine fibroids. Over 40% of respondents without uterine fibroids (control) consume vegetables and fruits very often, compared to only 28.9% in respondents with uterine fibroids. This relationship was statistically significant with p value of 0.045. Presence of hypertension was more frequent in respondents with uterine fibroids. 12.2% of the cases were found to be hypertensive compared to only 2.2% of the control. Those with fibroids were about six times more likely to have hypertension as those without fibroids.

As shown in Table 3, the mean Angiotensin 11 serum concentration and the mean systolic blood pressure were significantly higher in the study group when compared to the control group, with p value <0.001. The mean serum Angiotensin 11 level in the study group was 0.71± 0.07ng/ml, which was more than threefold higher than the mean of 0.23±0.07 ng/ml in the control group. Similarly the mean systolic blood pressure in the study group was 122.99±16.01mmhg, while that in the control group was 112.92±13.22mmhg.

Table 3: Relationship between the Mean Differences of Continuous Variables and Presence of Uterine Fibroid

Variable	Case group	Control group	t	p
Age of respondents	38.34±7.16	37.52±7.04	0.777	0.438
Parity	0.72±1.48	0.74±1.29	0.108	0.914
Number of years				
since last delivery	11.5±6.95	8.58±5.57	1.696	0.096
Age at Menarche	14±1.71	14.5±1.89	1.864	0.064
Age at 1st delivery	24.14±5.29	26.61±5.08	1.720	0.091
Weight in Kg	71.08±12.43	70.35±14.99	0.355	0.723
Height in metres	1.63±0.06	1.64±0.06	1.288	0.199
BMI	26.77±4.76	26.09±5.54	0.882	0.379
Systolic BP	122.99±16.01	112.92±13.22	4.598	<0.001
Diastolic BP	75.33±9.09	72.89±8.76	1.837	0.068
Ang.II in ng/ml	0.71±0.07	0.23±0.07	46.976	<0.001

Table 4 shows the relationship between the mean size of uterine fibroid in weeks and the presence of hypertension. The eleven respondents with uterine fibroids and hypertension had a mean uterine size of 21.45±3.47 weeks, compared to a mean size of 20.00±6.84 weeks among those without hypertension. This relationship was not statistically significant with p value of 0.492.

Table 4: Relationship between Uterine Size in Weeks and Hypertension

Variable Hypertension	N	Mean	t	p
Yes	11	21.45±3.47	0.690	0.492
No	79	20.00±6.84		

Discussion

The aetiology of uterine fibroids is not completely known despite its high prevalence in women. The theory that angiotensin II may be responsible or implicated in the aetiopathogenesis of uterine fibroids is intriguing and motivated this study.

The mean serum level of angiotensin II in women with uterine fibroids in this study was significantly three times higher than that found in women without uterine fibroids. This finding was not unexpected because previous studies have implicated angiotensin 2 in the aetiopathogenesis of uterine fibroids. Kirschen et al in their study found uterine fibroids to be more common in hypertensive patients implicated in angiotensin II in the aetiopathogenesis of both hypertension and uterine fibroids [12]. Isobe et al were also able to demonstrate in vitro that angiotensin II is involved in the aetiopathogenesis of uterine fibroids in rats. It was discovered that telmisartan and losartan both inhibited fibroid cell proliferation, Fisher et al also discovered that ACE inhibitors use, reduces the risk of developing clinically diagnosed leiomyoma in adult hypertensive women [11,13].

The concentration of angiotensin11 found in this study control population is much higher than the previously reported normal blood value. The value is about 10 times higher than the value of 2.4mug/100ml which is equivalent to 0.024ng/ml in normal non-hypertensive population reported by Catt et al and about six times higher than the value of 0.039ng/ml reported in normal subjects by Hermann et al [19,20]. This may be due to the sensitivity of

the different kits used. The mentioned studies were carried out in Caucasians with lesser risk of uterine fibroid and hypertension and were therefore expected to have lower angiotensin II levels when compared to blacks [21].

This study has shown that uterine fibroids are associated with an increased risk of hypertension. The commonest explanation for this relationship is that of reverse causality, which states that compression of the ureters by the expanding pelvic mass leads to the development of hypertension [18]. This plausible explanation has however been challenged severally before Haan suggested a direct causality between hypertension and uterine fibroids in a cross-sectional study where they found hypertension requiring medication and hypertension diagnosed at ages less than 35years amongst women with uterine fibroids [6,11,13]. Similarly, uterine fibroid was associated with systolic blood pressure in this study. This finding supports the cellular injury hypothesis because higher systolic blood pressure is related to higher pulse pressure which has been shown to be associated with more cellular injury [12,13]. In contrast, Boynton-Jarrett et al. found that fibroid incidence was higher in women with higher diastolic blood pressure [22].

This present study has also shown no significant difference in the mean angiotensin II concentrations in women with uterine fibroids who have hypertension and those who don't, although the mean angiotensin II concentration in both cases is much higher than that of the control group. This lack of difference further supports the suggestion that hypertension and uterine fibroids aetiology may share a common pathway involving angiotensin II [11,13,14].

The higher levels of angiotensin II in this study may also help to explain why hypertension and uterine fibroids are commoners in blacks [6,8,9,11] . It is also too early to completely discard the possibility of uterine fibroid also compressing the genitourinary system, despite there being no significant difference in the mean uterine size in respondents with uterine fibroids plus hypertension and those without hypertension.

Irrespective of which condition is responsible for the other, it is clear from findings in this study that an increased level of angiotensin II is associated with both uterine fibroid and hypertension. More studies are therefore urgently needed to further substantiate this finding because of the potential of being able to prevent both hypertension and uterine fibroid by administration of ACE Inhibitors and angiotensin II receptor blockers.

Conclusion

This study has shown that an increase in angiotensin II concentration is associated with uterine fibroids and hypertension. The fact that angiotensin II is associated with both fibroids and hypertension has a lot of potential, which may be employed in prevention programs for hypertension and uterine fibroids.

Ethical Approval and Consent

Ethical approval was obtained from the Health Research Ethics and Committee of the Lagos State University Teaching Hospital. The study was carried out according to the declaration of Helsinki The participants consented to participating in the study after being informed of the study.

Data Availability: The authors confirm that the data supporting the findings of this study are available within the article [and/or] its supplementary materials.

Financial Support and Sponsorship: nil

Acknowledgement: To all authors of references

Conflict of Interest: nil

Authors' Contribution: O.O conceived and designed the study, collected data T.K wrote the first draft. A.I, F.A, A.S and O.O participated in the design of the study, interpretation of data. ..A .S collected and analysed samples . F.A, O.O, TK critically reviewed for content and all authors approved the final manuscript.

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