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ORIGINAL STUDY

Effect of free androgen index on blood pressure variability and target organ damage in postmenopausal hypertensive women: findings from a cross-sectional study

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Abstract

Objective: The present study investigated the effects of free androgen index (FAI) on ambulatory blood pressure (ABP) and target organ function in postmenopausal hypertensive women.

Methods: A total of 285 postmenopausal hypertensive women (mean age 54.06 ± 3.61) were admitted to the Department of Hypertension of Lanzhou University Second Hospital between December 2018 and December 2020. According to the serum FAI level, the participants were divided into a low-FAI (<0.15) group, a medium-FAI (0.15-0.2) group, and a high-FAI (>0.2) group. The relationship of FAI with 24-hour ABP, left ventricular mass index (LVMI), and cardio-ankle vascular index (CAVI) was analyzed.

Results: The LVMI, CAVI, 24-hour mean systolic blood pressure (SBP), 24-hour SBP coefficient of variation and 24-hour SBP standard deviation, 24-hour SBP average real variation (ARV), and 24-hour diastolic blood pressure (DBP) ARV in high-FAI group were significantly higher than those in low- and medium-FAI groups ($P < 0.05$). After adjusting for confounding factors, partial correlation analysis showed that FAI was positively correlated with LVMI ($r = 0.728$, $P < 0.001$), CAVI (left: $r = 0.718$, $P < 0.001$; right: $r = 0.742$, $P < 0.001$), 24-hour SBP ARV ($r = 0.817$, $P < 0.001$), and 24-hour DBP ARV ($r = 0.747$, $P < 0.001$). After adjusting for confounding factors, it was found that LVMI increased by 17.64 g/m^2 for every 1 unit increase in FAI. CAVI also increased by 8.983 for every additional unit of FAI. In addition, the results also showed that LVMI and CAVI decreased respectively by 0.198 g/m^2 and 0.009 for every 1 unit increase in sex hormone–binding globulin. Multivariable linear regression showed that FAI was an independent risk factor for 24-hour SBP ARV (OR: 20.416, 95% CI 8.143-32.688, $P = 0.001$) and 24-hour DBP ARV (OR: 16.539, 95% CI 0.472-32.607, $P = 0.044$). The results also showed that sex hormone–binding globulin was an independent factor of 24-hour SBP ARV (OR: −0.022, 95% CI −0.044 to 0.000, $P = 0.048$) and 24-hour DBP-ARV (OR: −0.018, 95% CI −0.029 to −0.008, $P = 0.001$).

Conclusion: Higher serum FAI levels in postmenopausal hypertensive women indicate abnormal BP regulation and more serious target organ damage. FAI is closely related to 24-hour SBP ARV and 24-hour DBP ARV in postmenopausal hypertensive women.

Key Words: Blood pressure variability – Free androgen index – Postmenopausal hypertension – Target organ damage.

The occurrence of hypertension and hypertension-mediated organ damage (HMOD) in postmenopausal women is related to female sex hormone alterations.[1,2] Many large clinical studies have, however, demonstrated that it is not enough to explain the development and progression of postmenopausal hypertension and HMOD only from the

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perspective of decrease in estrogen level.[3,4] Change in androgen level due to ovarian interstitial hyperplasia and high level of circulating gonadotropin secretion are also important factors affecting hypertension and HMOD in postmenopausal women.[5,6]

Most human circulating testosterone exists in combination with sex hormone–binding globulin (SHBG) and has no biological activity.[7] Only 1% to 2% free testosterone and partial testosterone bound to albumin have biological effects.[8,9] It is reported that the free androgen index (FAI) based on the ratio of total testosterone to SHBG is a good clinical indicator reflecting the biological activity of androgen in vivo.[10]

The prevalence of hypertension and HMOD in postmenopausal women is significantly higher than that in premenopausal women.[11,12] Most studies have, however, focused on the correlation between serum total testosterone and hypertension in men.[13-15] Few studies have reported the role of actual biologically functional tissue-utilizable testosterone in blood pressure variability (BPV) and HMOD in postmenopausal hypertensive women. In addition, most studies have shown that exogenous androgen levels increase the risk of cardiovascular disease.[16] But whether endogenous androgen levels can be used as a risk factor for the occurrence of postmenopausal hypertension and HMOD has not been fully studied. The aim of the present study is to explore the relationship of different serum FAI levels with BPV and HMOD in postmenopausal hypertensive women and provide new predictive indicators and theoretical basis for research and prevention of HMOD in postmenopausal hypertensive women.

METHODS

Study population

This study enrolled 285 postmenopausal hypertensive women who were admitted to the Department of Hypertension of Lanzhou University Second Hospital (Lanzhou, China) between December 2018 and December 2020. According to the serum FAI level obtained by trichotomic analysis, the participants were divided into a low-FAI (<0.15) group, a medium-FAI (0.15-0.2) group, and a high-FAI (>0.2) group. This cross-sectional study was reviewed and approved by the Ethics Review Committee of Lanzhou University Second Hospital (2020A-283). Participants and their family members were informed of the study content and signed informed consent.

Inclusion and exclusion criteria

Inclusion criteria for this study were participants (1) aged 45 to 65 years; (2) who conformed to the diagnostic criteria of hypertension in postmenopausal women; and (3) with complete clinical data. Exclusion criteria for this study were participants (1) with a definite premenopausal diagnosis of hypertension or who were administered with antihypertensive medications; (2) with secondary hypertension and refractory hypertension; (3) with a history of hysterectomy or bilateral ovariectomy; (4) who received any form of hormone therapy; (5) with other severe systemic diseases, malignant tumors, neurological, or psychological disorders; and (6) who participated in other clinical studies.

Diagnostic criteria

In this study, menopause was defined as the permanent cessation of menstruation as a retrospective clinical diagnosis, and menopausal women were defined as women older than 40 years who had no menstruation for 12 months after their last menstruation and had serum follicle-stimulating hormone of more than 40 U/L and estradiol (E2) level less than 30 pg/mL. The diagnostic criteria for hypertension were based on the 2018 European Society of Cardiology/European Society of Hypertension guidelines for the management of arterial hypertension.[17] Postmenopausal hypertension was defined as hypertension occurring 1 year after female physiological menopause.

Baseline data collection and laboratory testing

Basic patient information was collected including age, weight, height, waist circumference, hip circumference, educational background, family history of hypertension, and the duration of hypertension. Body mass index (BMI) and waist-to-hip ratio were measured by BMI = weight/height^2, and waist-to-hip ratio = waist circumference/hip circumference. Morning fasting venous blood was collected and centrifuged at 4,000 rpm for 15 minutes. Serum total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol, blood urea nitrogen (BUN), and creatinine (CR) were detected using an automatic biochemical instrument (Roche Cobas C501, Basel, Switzerland). Serum testosterone level was detected by electrochemiluminescence (CobasE-601, Basel, Switzerland). Serum SHBG level was determined by ELISA. FAI was the ratio of serum testosterone to SHBG.

Ambulatory blood pressure (ABP) test

Twenty-four-hour ABP was measured using an automatic portable ABP monitor. In this study, daytime was programmed from 6:00 to 22:00 and BP was measured every 30 minutes. Nighttime was from 22:00 to 6:00 the next day, and BP was measured once every 60 minutes. More than 80% of the effective measurement times were considered as valid data. The following parameters were recorded round the clock in all participants: (1) mean systolic blood pressure (SBP) and corresponding standard deviation (SD); (2) average diastolic blood pressure (DBP) and corresponding SD. The following indexes were obtained according to the calculation formula: (1) average real variation (ARV)= $\frac{1}{N-1}\sum_{k-1}^{N-1}|BP_{k+1}-BP_k|$; (2) coefficient of variation (CV) = SD/mean value.

Assessment of left ventricular mass and vascular function

Left ventricular end-diastolic diameter (LVEDd), interventricular septal thickness (IVST) and left ventricular posterior wall thickness (LVPWT) were recorded using the GE Vivid7 ultrasonic diagnostic instrument. According to Devereux

formula, the left ventricular mass index (LVMI) was calculated as follows: LVM = 0.8 × 1.04 × [(LVEDd + interventricular septal thickness + LVPWT)^3 − LVEDd^3] + 0.6; body surface area (female) = 0.0073 × height + 0.0127 × weight − 0.2106; LVMI = LVM/body surface area. Vascular sclerosis was examined using the MB3000 arteriosclerosis detector. The cardio-ankle vascular index (CAVI), an indicator of arterial elasticity and atherosclerosis, was recorded. After at least 15 minutes of rest on her back, professionals placed appropriately sized cuffs on the participant's upper arms and ankles, respectively. Electrocardiogram electrodes were installed on both wrists and the heart sound sensor was attached to the sternum in the second intercostal space. The knee pulse sensor was mounted on the participant's knee and the airbag was aligned with the center of the popliteal fossa. After entering the participant's information, the machine automatically measured and calculated the CAVI value. CAVI = a [(2ρ/ΔP) × ln(Ps/Pd)PWV2] + b (where ρ: blood viscosity, Ps: SBP, Pd: DBP, ΔP: Ps − Pd, PWV: pulse wave velocity.)

Statistical method

SPSS20.0 statistical software was used for data analysis. PASS15.0 software and sample size estimation principle of regression analysis were used to calculate the sample size. The principle was that 10 participants are required for each variable. The least sample size required in this study is 260. Continuous variables were tested for normality and homogeneity of variance. Data consistent with normal distribution are expressed as the mean ± SD and ANOVA test was used for comparison between groups. Non-normal distribution data are represented as median and quartile, and the Kruskal-Wallis test was used for comparison between groups. Categorical variables are expressed as percentages and comparison between groups was performed by the chi-square test. The correlation between serum FAI level and BPV, vascular function, and cardiac damage in postmenopausal hypertensive women was analyzed by partial correlation method. Multiple linear regression was used to analyze the impact of various factors on SBP ARV and DBP ARV in postmenopausal hypertensive women. P less than 0.05 was considered statistically significant.

RESULTS

General data about postmenopausal hypertension with different FAI levels

This study included 285 postmenopausal hypertensive women with a mean age of 54.06 ± 3.61 years, in whom 92 (32%), 98 (34%), and 95 (33%) participants showed low, medium, and high FAI levels, respectively. Compared with participants in the low-FAI group, participants in the medium- and high-FAI groups had significantly higher TC levels ($P < 0.05$). There were no significant differences in age, BMI, educational background, family history of hypertension, TG, low-density lipoprotein cholesterol, BUN, and CR between different FAI groups ($P > 0.05$) (Table 1).

Comparison of 24-hour ambulatory blood pressure in postmenopausal hypertensive women

The 24-hour mean SBP, 24-hour SBP SD, and 24-hour SBP CV in the high-FAI group were significantly higher than those in the low- and medium-FAI groups ($P < 0.05$). The 24-hour SBP ARV and 24-hour DBP ARV in the high-FAI group were significantly higher than those in the other two groups ($P < 0.05$) (Table 2).

TABLE 1. *General data about postmenopausal hypertension with different free androgen index levels*

	FAI <0.15 (n = 92)	FAI 0.15-0.2 (n = 98)	FAI >0.2 (n = 95)	
Age	54.32 ± 3.72	54.35 ± 3.49	53.62 ± 3.57	0.18
BMI (kg/m^2)	23.99 ± 3.24	24.36 ± 3.32	24.01 ± 3.20	0.32
WHR	0.84 ± 0.08	0.84 ± 0.06	0.84 ± 0.07	0.35
Educational level (college degree or above), n (%)	36 (39)	26 (27)	46 (48)	0.17
The duration of hypertension	3.30 ± 2.65	3.58 ± 2.93	3.93 ± 2.39	0.18
Family history of hypertension, n (%)	64 (70)	43 (44)	57 (60)	0.18
Current antihypertensive drugs				
ACEI, n (%)	13 (14)	17 (17)	21 (22)	0.17
ARB, n (%)	32 (35)	38 (39)	36 (38)	0.09
Beta-blockers, n (%)	6 (7)	4 (4)	13 (14)	0.13
CCB, n (%)	62 (67)	45 (46)	74 (78)	0.11
Diuretic, n (%)	25 (27)	18 (18)	17 (18)	0.18
TC (mmol/L)	4.60 ± 0.81	4.73 ± 0.76	4.97 ± 0.74[a]	0.02
TG (mmol/L)	1.47 (0.98-1.94)	1.45 (1.05-1.98)	1.36 (1.05-1.73)	0.29
LDL-C (mmol/L)	2.56 ± 0.65	2.50 ± 0.57	2.63 ± 0.66	0.20
BUN (mmol/L)	4.71 ± 1.27	4.66 ± 1.24	4.62 ± 1.14	0.37
CR (μmol/L)	59.58 ± 10.88	61.77 ± 8.64	60.81 ± 8.60	0.18
T (ng/dL)	16.95 ± 3.06	21.13 ± 3.39[a]	24.47 ± 3.34[a,b]	0.00
SHBG (nmol/L)	130.81 ± 15.32	125.22 ± 18.29	116.96 ± 16.88[a,b]	0.03

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BUN, blood urea nitrogen; CR, creatinine; CCB, calcium channel blocker; FAI, free androgen index; LDL-C, low-density lipoprotein cholesterol; SHBG, sex hormone–binding globulin; T, testosterone; TC, total cholesterol; TG, triglyceride; WHR, waist-to-hip ratio.
[a]Observed significance $P < 0.05$ compared with FAI <0.15 group.
[b]Observed significance $P < 0.05$ compared with FAI 0.15-0.2 group.

TABLE 2. *Comparison of 24-hour ambulatory blood pressure in postmenopausal hypertensive women*

	FAI<0.15 ($n=92$)	FAI 0.15-0.2 ($n=98$)	FAI >0.2 ($n=95$)	Adjusted P value
Daytime mean SBP (mmHg)	140.07 ± 10.70	144.42 ± 11.21	168.11 ± 14.85[a]	0.03
Daytime mean DBP (mmHg)	86.20 ± 11.64	84.54 ± 10.49	83.66 ± 10.02	0.09
Nighttime mean SBP (mmHg)	136.62 ± 15.90	134.43 ± 13.80	133.34 ± 15.24	0.10
Nighttime mean DBP (mmHg)	79.65 ± 12.31	78.47 ± 8.69	76.11 ± 10.82[a]	0.03
24-h mean SBP (mmHg)	137.73 ± 9.90	141.19 ± 10.44[a]	145.21 ± 11.84[a,b]	0.00
24-h mean DBP (mmHg)	83.79 ± 9.64	82.92 ± 9.31	81.58 ± 9.51	0.09
24-h SBP CV (%)	12.05 ± 2.86	13.24 ± 3.54[a]	14.59 ± 4.50[a,b]	0.00
24-h DBP CV (%)	13.92 ± 3.14	14.21 ± 3.30	14.40 ± 3.56	0.17
24-h SBP SD	16.66 ± 4.16	18.63 ± 5.01[a]	21.08 ± 6.49[a,b]	0.00
24-h DBP SD	11.55 ± 2.65	11.74 ± 2.72	11.60 ± 2.61	0.24
24-h SBP ARV	11.40 ± 1.13	14.49 ± 1.11[a]	18.46 ± 3.74[a,b]	0.00
24-h DBP ARV	5.09 ± 1.27	6.22 ± 0.79[a]	7.65 ± 1.37[a,b]	0.00

ARV, average real variation; DBP, diastolic blood pressure; CV, coefficient of variation; FAI, free androgen index; SBP, systolic blood pressure; SD, standard deviation.
[a]Observed significance $P < 0.05$ compared with FAI <0.15 group.
[b]Observed significance $P < 0.05$ compared with FAI 0.15-0.2 group.

TABLE 3. *Comparison of target organ damage in postmenopausal hypertensive women*

	FAI <0.15 ($n=92$)	FAI 0.15-0.2 ($n=98$)	FAI >0.2 ($n=95$)	P
Proteinuria, n (%)	0 (0)	1 (1)	3 (3)	0.08
CAVI (left)	7.02 ± 0.76	7.57 ± 0.82[a]	8.75 ± 0.95[a,b]	0.00
CAVI (right)	7.04 ± 0.53	7.88 ± 0.49[a]	8.67 ± 0.72[a,b]	0.00
LVMI	67.97 ± 9.88	84.86 ± 4.52[a]	98.43 ± 1.29[a,b]	0.00

CAVI, cardio-ankle vascular index; FAI, free androgen index; LVMI, left ventricular mass index.
[a]Observed significance $P < 0.05$ compared with FAI <0.15 group.
[b]Observed significance $P < 0.05$ compared with FAI 0.15-0.2 group.

Comparison of target organ damage in postmenopausal hypertensive women

As shown in Table 3, LVMI in the high-FAI group was significantly larger than that in the other two groups ($P < 0.05$). The CAVI (left) level in low- and medium-FAI groups was significantly lower than that in the high-FAI group ($P < 0.05$). There was no significant difference in proteinuria and CAVI (right) between the three groups ($P > 0.05$).

Correlation analysis of FAI with BPV, LVMI, and CAVI

After correcting for age, BMI, the duration of hypertension, current antihypertensive drugs, TC, TG, BUN, and CR confounding factors, the results of partial correlation analysis showed that FAI level in postmenopausal hypertensive women was positively correlated with 24-hour SBP ARV ($r = 0.817$, $P < 0.001$), 24-hour DBP ARV ($r = 0.747$, $P < 0.001$), LVMI ($r = 0.728$, $P < 0.001$), and CAVI (left:

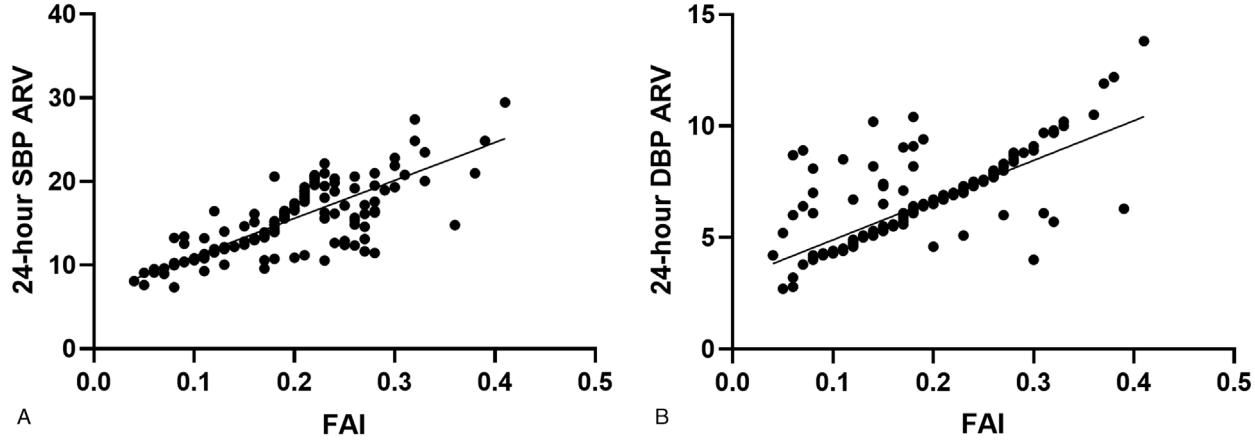

FIG. 1. Scatter diagram of the correlation between FAI and 24-hour SBP ARV and 24-hour DBP ARV in postmenopausal hypertensive women. (**A**) The correlation between FAI and 24-hour SBP ARV was established and (**B**) the correlation between FAI and 24-hour DBP ARV was identified in postmenopausal hypertensive women. ARV, average real variation; DBP, diastolic blood pressure; FAI, free androgen index; SBP, systolic blood pressure.

TABLE 4. *Multivariable regression analysis of free androgen index, left ventricular mass index, and cardio-ankle vascular index in postmenopausal hypertension*

	Regression coefficient and 95% CI	*P*
LVMI		
Model 1	18.212 (16.180-20.243)	<0.001
Model 2	18.388 (16.338-20.438)	<0.001
Model 3	17.643 (15.482-19.795)	<0.001
CAVI		
Model 1	9.099 (7.665-10.533)	<0.001
Model 2	8.947 (7.482-10.413)	0.003
Model 3	8.983 (7.422-10.524)	0.008

Model 1: no adjustment; Model 2: adjusted for age, BMI, the course of hypertension, family history of hypertension, current antihypertensive drug, and serological indexes; Model 3: Model 1+ Model 2+ the 24-hour mean systolic blood pressure + the 24-hour mean diastolic blood pressure.
BMI, body mass index; CAVI, cardio-ankle vascular index; FAI, free androgen index; LVMI, left ventricular mass index.

TABLE 5. *Multivariable regression analysis of sex hormone–binding globulin: left ventricular mass index and cardio-ankle vascular index in postmenopausal hypertension*

	Regression coefficient and 95% CI	*P*
LVMI		
Model 1	−0.239 (−0.349 to −0.129)	<0.001
Model 2	−0.226 (−0.336 to −0.115)	<0.001
Model 3	−0.198 (−0.306 to −0.091)	<0.001
CAVI		
Model 1	−0.014 (−0.021 to −0.007)	<0.001
Model 2	−0.013 (−0.020 to −0.006)	<0.001
Model 3	−0.009 (−0.016 to −0.003)	<0.001

Model 1: no adjustment; Model 2: adjusted for age, BMI, the course of hypertension, family history of hypertension, current antihypertensive drug, and serological indexes; Model 3: Model 1 + Model 2 + the 24-hour mean systolic blood pressure + the 24-hour mean diastolic blood pressure.
BMI, body mass index; CAVI, cardio-ankle vascular index; LVMI, left ventricular mass index; SHBG, sex hormone–binding globulin.

$r = 0.718$, $P < 0.01$; right: $r = 0.742$, $P < 0.001$). The scatter plot showed a significant correlation of FAI with 24-hour SBP ARV and 24-hour DBP ARV (Fig. 1).

Multivariable regression analysis of FAI, SHBG and LVMI, and CAVI in postmenopausal hypertension

After correcting for age, BMI, the duration of hypertension, family history of hypertension, current antihypertensive drug, serological indexes, the 24-hour mean SBP, and the 24-hour mean DBP confounding factors by various models, multiple linear regression was used to further explore the correlation between FAI, LVMI, and CAVI. After adjusting for confounding factors, it was found that LVMI increased by $17.64\ g/m^2$ for every 1 unit increase in FAI. In addition, CAVI also increased by 8.983 for every additional unit of FAI (Table 4). In addition, multiple linear regression also showed that LVMI and CAVI, respectively decreased by $0.198\ g/m^2$ and 0.009 for every 1 unit increase in SHBG (Table 5).

Multivariable regression analysis of FAI, SHBG, 24-hour SBP ARV, and 24-hour DBP ARV in postmenopausal hypertension

After adjusting for age, BMI, the duration of hypertension, family history of hypertension, current antihypertensive drugs, and serological indexes, the results of multivariate linear regression showed that FAI was an independent factor of 24-hour SBP ARV (odds ratio [OR]: 20.416, 95% CI 8.143-32.688, $P = 0.001$) and 24-hour DBP-ARV (OR: 16.539, 95% CI 0.472-32.607, $P = 0.044$) after adjusting for positive confounding factors. The results are shown in Table 6. In addition, results in Table 7 also show that SHBG was an

TABLE 6. *Multivariable regression analysis of free androgen index and 24-hour systolic blood pressure average real variation, 24-hour diastolic blood pressure average real variation in postmenopausal hypertension*

Related factor (FAI)	24-h SBP ARV	24-h SBP CV	24-h SBP SD	24-h DBP ARV	24-h DBP CV	24-h DBP SD
β	0.426	0.204	0.211	0.642	0.199	0.232
P value	0.001	0.515	0.489	0.044	0.537	0.473
Regression Coefficient	20.416	11.767	17.794	16.539	9.719	9.202
95% CI	8.143-32.688	−23.822 to 47.356	−32.840 to 68.482	0.472-32.607	−21.265 to 40.704	−16.043 to 34.447

Adjusted for age, body mass index (BMI), the course of hypertension, family history of hypertension, current antihypertensive drug, and serological indexes in multivariable regression model.
ARV, average real variation; CV, coefficient of variation; DBP, diastolic blood pressure; FAI, free androgen index; SBP, systolic blood pressure; SD, standard deviation.

TABLE 7. *Multivariable regression analysis of sex hormone–binding globulin and 24-hour systolic blood pressure average real variation, 24-hour diastolic blood pressure average real variation in postmenopausal hypertension*

Related factor (FAI)	24-h SBP ARV	24-h SBP CV	24-h SBP SD	24-h DBP ARV	24-h DBP CV	24-h DBP SD
β	−0.102	−0.002	−0.018	−0.199	0.045	0.052
P	0.048	0.972	0.763	0.001	0.728	0.406
Regression coefficient	−0.022	0.000	−0.006	−0.018	0.008	0.008
95% CI	−0.044 to 0.000	−0.027 to 0.026	−0.044 to 0.032	−0.029 to −0.008	−0.014 to 0.031	−0.011 to 0.026

Adjusted for age, body mass index (BMI), the course of hypertension, family history of hypertension, current antihypertensive drug, and serological indexes in multivariable regression model.
ARV, average real variation; CV, coefficient of variation; DBP, diastolic blood pressure; FAI, free androgen index; SBP, systolic blood pressure; SD, standard deviation; SHBG, sex hormone–binding globulin.

independent factor of 24-hour SBP ARV (OR: −0.022, 95% CI −0.044 to 0.000, $P = 0.048$) and 24-hour DBP-ARV (OR: −0.018, 95% CI −0.029 to −0.008, $P = 0.001$).

DISCUSSION

To the best of our knowledge, this is the first study to evaluate the relationship of serum FAI with BPV and HMOD in postmenopausal hypertensive women. We found that FAI was independently positively correlated with 24-hour SBP ARV and 24-hour DBP ARV. In addition, abnormal BP regulation and target organ damage became more serious in postmenopausal hypertensive women with higher serum FAI level.

As mentioned earlier, free testosterone is an effective substance that exerts biological effects in the body.[18,19] Equilibrium dialysis and ammonium sulfate precipitation are two common methods for direct measurement of free testosterone at present. However their clinical application is limited by high costs, time consumption, and strict technical requirements.[20] Studies have demonstrated that FAI is a better clinical indicator that reflects the biological activity of testosterone in the body, and to some extent is a measure of testosterone after correction of abnormal SHBG.[21] In a 29-month follow-up study of postmenopausal women without obvious cardiovascular disease or diabetes, it was found that FAI was significantly associated with new-onset hypertension, decreased pulse wave velocity, and increased SBP and DBP.[22] Zhou et al[23] found that the FAI level of Chinese women was higher than that of White women. Even after adjusting for confounding factors, higher FAI levels were associated with cardiovascular risk factors. Georgiopoulos et al[24] also noted that FAI may be a biomarker for cardiovascular disease risk in postmenopausal women. The results of our study showed that participants in the high-FAI group had significantly abnormal BPV and increased CAVI as compared with participants in the low and medium FAI groups, suggesting that postmenopausal hypertensive women in medium- and high-FAI groups sustained more serious abnormal BP regulation and arterial stiffness. The possible reason for the above phenomenon is that increased androgens through specific arterial wall androgenic receptors lead to vascular inflammation and endothelial dysfunction, resulting in changes in vascular tone and wall composition which may directly affect arterial wall stiffness and abnormal blood pressure regulation.

It is worth noting that after controlling for confounders, FAI was an independent predictor of 24-hour SBP ARV and 24-hour DBP ARV. However, we did not find a significant correlation of FAI with SD and CV, two traditional indicators reflecting BPV. This is probably due to the following reasons. First, SD only reflects BP dispersion around the mean value, and does not specify the time sequence of the BP values obtained.[25] Second, ARV is the absolute difference between consecutive SBP or DBP measurements within 24 hours, which can indicate the trend of BP changes over time.[26] In addition, ARV better reflects the damage to the cardiovascular system caused by additional and intermittent stress. A study involving more than 8,000 hypertensive participants[27] showed that 24-hour ARV had better predictive significance for mortality, cardiovascular events, and stroke than SD. Another study involving hypertensive women older than 55 years[28] suggested that the relative risk of cardiovascular adverse events in the high-ARV group was 4.548 compared with the low ARV group. All these studies suggested that ARV was superior to SD in evaluating BPV and independently associated with cardiovascular events.

This is the first study to investigate the relationship between endogenous free testosterone and BPV and target organ damage in postmenopausal women with hypertension. In addition, the analysis was adjusted for potential confounders, including demographic characteristics, history of hypertension, the course of hypertension, family history of hypertension, current antihypertensive drug, and serological indexes. Some limitations in this study should also be considered. Firstly, because it was a cross-sectional study, the main limitation was the inability to identify temporality, making it difficult to clarify the causal relationship and mechanism between FAI and HMOD. Furthermore, although electrochemiluminescence is a commonly used method for hormone detection in clinical practice, it is still slightly inferior to liquid chromatography-mass spectrometry. Finally, participants were recruited from a single center, and multicenter studies are needed to further confirm the current research results in the future.

CONCLUSION

Serum FAI level was positively correlated with 24-hour SBP ARV and 24-hour DBP ARV in postmenopausal hypertensive women, which was not affected by other confounding factors. The high level of FAI in postmenopausal hypertensive women was associated with abnormal BPV and severe target organ damage.

REFERENCES

1. Shawky NM, Patil CN, Dalmasso C, et al. Pregnancy protects hyperandrogenemic female rats from postmenopausal hypertension. *Hypertension* 2020;76:943-952.
2. Guivarc'h E, Favre J, Guihot A-L, et al. Nuclear activation function 2 estrogen receptor α attenuates arterial and renal alterations due to aging and hypertension in female mice. *J Am Heart Assoc* 2020;9:1-17.
3. Grodstein F, Manson JE, Stampfer MJ. Hormone therapy and coronary heart disease: the role of time since menopause and age at hormone initiation. *J Womens Health (Larchmt)* 2006;15:35-44.
4. Grady D, Herrington D, Bittner V, et al. Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). *JAMA* 2002;288:49-57.
5. Couzinet B, Meduri G, Lecce MG, et al. The postmenopausal ovary is not a major androgen-producing gland. *J Clin Endocrinol Metab* 2001;86:5060-5066.
6. Markopoulos MC, Kassi E, Alexandraki KI, Mastorakos G, Kaltsas G. Hyperandrogenism after menopause. *Eur J Endocrinol* 2015;172:R79-R91.
7. Round P, Das S, Wu TS, Wahala K, Van Petegem F, Hammond GL. Molecular interactions between sex hormone-binding globulin and nonsteroidal ligands that enhance androgen activity. *J Biol Chem* 2020;295:1202-1211.
8. G, Keevil BG, Adaway J. Assessment of free testosterone concentration. *J Steroid Biochem Mol Biol* 2019;190:207-211.

9. Goldman AL, Bhasin S, Wu FCW, Krishna M, Matsumoto AM, Jasuja R. A reappraisal of testosterone's binding in circulation: physiological and clinical implications. *Endocr Rev* 2017;38:302-324.
10. Georgiopoulos GA, Lambrinoudaki I, Athanasouli F, et al. Free androgen index as a predictor of blood pressure progression and accelerated vascular aging in menopause. *Atherosclerosis* 2016;247:177-183.
11. Sherman SB, Sarsour N, Salehi M, et al. Prenatal androgen exposure causes hypertension and gut microbiota dysbiosis. *Gut Microbes* 2018;9:400-421.
12. Brahmbhatt Y, Gupta M, Hamrahian S, et al. Hypertension in premenopausal and postmenopausal women. *Curr Hypertens Rep* 2019;21:74.
13. Yang Q, Li Z, Li W, et al. Association of total testosterone, free testosterone, bioavailable testosterone, sex hormone-binding globulin, and hypertension. *Medicine* 2019;98:e15628.
14. Jiang Y, Ye J, Zhao M, et al. Cross-sectional and longitudinal associations between serum testosterone concentrations and hypertension: Results from the Fangchenggang Area Male Health and Examination Survey in China. *Clin Chim Acta* 2018;487:90-95.
15. Vlachopoulos C, Pietri P, Ioakeimidis N, et al. Inverse association of total testosterone with central haemodynamics and left ventricular mass in hypertensive men. *Atherosclerosis* 2016;250:57-62.
16. Boden WE, Miller MG, McBride R, et al. Testosterone concentrations and risk of cardiovascular events in androgen-deficient men with atherosclerotic cardiovascular disease. *Am Heart J* 2020;224:65-76.
17. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J* 2018;39:3021-3104.
18. Keevil BG, Adaway J. Assessment of free testosterone concentration. *J Steroid Biochem Mol Biol* 2019;190:207-211.
19. Li N, Ma R, Wang S. The potential role of testosterone in hypertension and target organ damage in hypertensive postmenopausal women. *Clin Interv Aging* 2019;14:743-752.
20. Rhea JM, French D, Molinaro RJ. Direct total and free testosterone measurement by liquid chromatography tandem mass spectrometry across two different platforms. *Clin Biochem* 2013;46:656-664.
21. Keevil BG, Adaway J, Fiers T, Moghetti P, Kaufman JM. The free androgen index is inaccurate in women when the SHBG concentration is low. *Clin Endocrinol* 2018;88:706-710.
22. Creatsa M, Armeni E, Stamatelopoulos K, et al. Circulating androgen levels are associated with subclinical atherosclerosis and arterial stiffness in healthy recently menopausal women. *Metabolism* 2012;61:193-201.
23. Zhou Z, Ni R, Hong Y, et al. Defining hyperandrogenaemia according to the free androgen index in Chinese women: a cross-sectional study. *Clin Endocrinol* 2012;77:446-452.
24. Georgiopoulos G, Kontogiannis C, Lambrinoudaki I, Rizos D, Stamatelopoulos K. Free androgen index as a biomarker of increased cardiovascular risk in postmenopausal women. *J Am Coll Cardiol* 2018;72:1986.
25. Sarah SL, Wood S, Koshiaris C, et al. Blood pressure variability and cardiovascular disease: systematic review and meta-analysis. *BMJ* 2016;354:i4098.
26. Mena LJ, Felix VG, Melgarejo JD, Maestre GE. 24-Hour blood pressure variability assessed by average real variability: a systematic review and meta-analysis. *J Am Heart Assoc* 2017;6:e006895.
27. Hansen TW, Thijs L, Li Y, et al. Prognostic value of reading-to-reading blood pressure variability over 24 hours in 8938 subjects from 11 populations. *Hypertension* 2010;55:1049-1057.
28. Mena L, Pintos S, Queipo NV, Aizpúrua JA, Maestre G, Sulbarán T. A reliable index for the prognostic significance of blood pressure variability. *J Hypertens* 2005;23:505-511.