

Testosterone association with blood pressure profile and left ventricular mass in a young hypertensive population

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Abstract

Sex hormones not only regulate the gonads function, but also may affect the cardiovascular system, although their role is still not clear. Testosterone influence on arterial pressure and left ventricular hypertrophy were widely reported. A number of factors have been implicated as the underlying cause of the relation between testosterone and blood pressure, including sex and age as most important ones. In present findings, a 24-hour ABPM revealed that 33.9% of patients had an altered pattern of blood pressure with no significant differences between sexes. In the whole studied sample, positive correlation has been found between testosterone and 24-hour systolic blood pressure, daytime BP, sodium and potassium levels in the 24-hour urine collection, and left ventricular mass index. In conclusion, testosterone association with blood pressure profile and left ventricular mass in a young hypertensive population seems to be probable, but further analysis is necessary.

Key words: testosterone, blood pressure

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Introduction

Sex hormones not only regulate the gonads' function but also may affect the cardiovascular system, although their role is still not clear [1–5].

Referring to the testosterone influence on arterial pressure, literature has known many mechanisms of which androgen-dependent gender differences were widely reported [3, 6]. Similarly, the relationship between testosterone levels and an unfavourable BP response for testosterone chronic supplementation driven by activation of renin-angiotensin system (RAS) [7, 8].

Since declining gonadal function with aging is known, age need be taken into account to examine the relationship between testosterone and blood pres-

sure [9, 10]. The results of previous studies performed in elderly and middle-aged patients indicate the association between testosterone levels and hypertension [1, 3, 9, 11]. Data in the young population are inadequate. The aim of this study was to explore the relationship between testosterone and blood pressure profile in young hypertensive patients.

Materials and methods

Study population

The study was carried out among patients with established diagnosis of essential hypertension treated at university-affiliated Department of Hypertension

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and Internal Medicine in Szczecin. Overall, we included 80 consecutive hypertensive patients (35 females, 45 males), mean age 29.9 ± 16.3 years. We excluded those patients who were treated with spironolactone, glucocorticoids, anabolic steroids, and oral contraception. We also evaluated 24-hour urinary potassium (normal range: 25–125 mmol/24h) and sodium (normal range: 40–220 mmol/24h) excretion. Based on medical history and medical records, we collected data on family cardiovascular burden, smoking habits, dyslipidaemia, chronic kidney disease, and type 2 diabetes.

Measurements

Anthropometric measurements were taken and body mass index (BMI) was calculated from the body weight and height. In all cases, we performed 24-hour blood pressure monitoring (ABPM) (Spacelabs Healthcare) and analysed 24-hour daytime and nocturnal systolic, diastolic, and mean blood pressure. Testosterone (normal range for men: 4.25–30.37 pg/ml; normal range for women: 0.04–4.18 pg/ml), PRA (normal range: 0.51–2.64 ng/ml/h) and plasma aldosterone (normal range: 10–160 pg/ml) were measured using commercially available assays. From these measurements we calculated the aldosterone-to-renin ratio (ARR). In reference to the current guidelines, the left ventricular mass index has been assessed in all cases [12]. Echocardiography was performed by using a GE Vivid S6 device [12].

Statistical analysis

Descriptive data are presented as mean \pm SD or numbers and percentage. When comparing normally distributed variables between groups of men and women, an independent *t* test was used for comparing means. For comparison of skewedly distributed variables between the study groups, median values were calculated and Mann-Whitney U and/or Kruskal-Wallis test was used. Categorical variables were evaluated by Chi square test. Correlations between the study variables were evaluated by Spearman's rank correlation. *P* values < 0.05 were considered significant. All analyses were carried out in Statistica version 12 (Statsoft, Poland).

Results

The main clinical and biochemical characteristics of the study sample are shown in Tables I–IV. Majority of subjects were overweight/obese. As many as 82.5% of patients had a positive family history of cardiovascular disease. Additionally, 42.3% were

Table I. Baseline clinical characteristics of the study population (*n* = 80)

	Mean value (\pm SD) Median (range)
Age (years)	29.9 \pm 16.3 30 (19.0–43.0)
BMI [kg/m ²]	28.6 \pm 6.2 27.5 (19.4–48.0)
Duration of hypertension (months)	45.6 \pm 57.3 24.0 (1.0–308.0)
SBP [mm Hg]	148.3 \pm 16.3 148 (114.0–190.0)
DBP [mm Hg]	109.9 \pm 12.4 90 (62.0–130.0)
MAP [mm Hg]	109.9 \pm 12.0 109.5 (83.3–146.7)
	% (n)
Women	43.7% (35)
Men	56.3% (45)
Smokers	42.3% (44)
Family CVD history	82.5% (66)
BMI < 25 kg/m ²	27.5% (22)
BMI \geq 25 < 30kg/m ²	41.3% (33)
BMI \geq 30kg/m ²	31.2% (25)

SD — standard deviation; BMI — body mass index; SBP — systolic blood pressure; DBP — diastolic blood pressure; MAP — mean arterial pressure

Table II. Selected echocardiographic parameters of the study population (*n* = 80)

	Mean (\pm SD) Median (range)
LVMI [g/m ²]	81.3 \pm 19.5 79.2 (18.7–136.7)
RWT	0.5 \pm 1.9 0.3 (0.2–17.2)
Septal velocity [cm/s]	12.3 \pm 3.1 12.0 (5.3–20.0)
Lateral velocity [cm/s]	15.6 \pm 3.4 15.3 (8.0–25.0)
LAVI [ml/m ²]	18.6 \pm 9.1 17.1 (2.4–87.4)
E/e' Ratio	5.9 \pm 2.2 5.7 (1.2–19.9)

LVMI — left ventricular mass index; RWT — relative wall thickness; E — early mitral inflow velocity; e' — mitral annular early diastolic velocity; LAVI — left atrium volume index

smokers. A 24-hour ABPM revealed that 33.9% of patients had an altered pattern of blood pressure (non-dipping, reverse-dipping, or extreme-dipping) with no significant differences between sexes. In the whole studied sample, positive correlation has been

Table III. Biochemical and hormonal characteristics of study population (n = 80)

	Mean (± SD) Median (range)
Serum sodium level [mmol/l]	141.0 ± 1.8 141.0 (136.0–145.0)
Serum potassium level [mmol/l]	4.4 ± 0.3 4.4 (3.7–5.1)
Sodium in 24h urine collection [mmol/24h]	183.7 ± 62.5 175.2 (73.0–361)
Potassium in 24h urine collection [mmol/24h]	54.0 ± 20.2 50.7 (17.0–141.0)
PRA [ng/ml/h]	1.5 ± 0.6 1.5 (0.6–3.2)
Aldosterone [pg/ml]	105.7 ± 36.5 108.0 (31.0–178.0)
ARR	7.1 ± 2.7 7.0 (1.4–17.2)
Testosterone [pg/ml]	10.4 ± 11.4 7.5 (0.6–70.2)

PRA — plasma renin activity; ARR — aldosterone/renin ratio

found between testosterone and 24-hour systolic blood pressure, daytime BP, sodium and potassium levels in the 24-hour urine collection, and left ventricular mass index (Table V). There was only weak negative correlation between total testosterone (TT) and nocturnal diastolic blood pressure ($p \leq 0.02$). Compared with female, men had significantly higher testosterone level, 24-hour and daytime systolic blood pressure and lower nocturnal diastolic blood pressure (Table VI). Testosterone level was inversely correlated with age. We did not find significant association between TT and non-dipping profile after adjusting for age.

Discussion

In the past decades, the associations between exogenous and endogenous testosterone (TT) and blood pressure (BP) in males and females have been extensively studied; however, inconsistent results have been obtained. In the present findings a 24-hour ABPM revealed that 33.9% of patients had an altered pattern of blood pressure (non-dipping, reverse-dipping, or extreme-dipping) with no significant differences between sexes. A positive correlation has been found between testosterone and 24-hour systolic blood pressure, daytime BP. This findings are in line with the general research trend [1, 11, 13, 14]. Literature suggests various mechanisms involved in the testosterone impact on blood pressure regulation.

Table IV. 24-hour ambulatory blood pressure monitoring parameters in study population (n = 80)

	Mean ± SD Median (range)
24 SBP [mm Hg]	126.2 ± 10.5 126.5 (102.0–177.0)
24 DBP [mm Hg]	75.9 ± 8.3 75.5 (53.0–109.0)
24 MAP [mm Hg]	92.2 ± 8.1 91.0 (76.0–132.0)
SBPd [mm Hg]	132.5 ± 12.1 129.0 (105.0–181.0)
DBPd [mm Hg]	78.7 ± 8.4 79.0 (54.0–111.0)
MAPd [mm Hg]	94.4 ± 12.8 94.0 (46.0–144.0)
SBPn [mm Hg]	114.9 ± 12.8 116.0 (80.0–140.0)
DBPn [mm Hg]	68.6 ± 10.5 67.0 (51.0–125.0)
MAPn [mm Hg]	83.0 ± 11.5 84.0 (42.0–121.0)
	% (n)
Dippers	66.1% (53)
Non-dippers	31.3 (25)
Reverse-dippers	1.3% (1)
Extreme-dippers	1.3% (1)

24 SBP — 24-hour systolic blood pressure; 24 DBP — 24-hour diastolic blood pressure; 24 MAP — 24-hour mean arterial pressure; SBPd — daytime systolic blood pressure; DBPd — daytime diastolic blood pressure; MAPd — daytime mean arterial pressure; SBPn — nocturnal systolic blood pressure; DBPn — nocturnal diastolic blood pressure; MAPn — nocturnal mean arterial pressure

In animal models, chronic testosterone supplements caused hypertension in male spontaneously hypertensive rats (SHR) and this unfavourable BP response was mainly driven by activation of renin-angiotensin system (RAS) [7]. In addition, prenatal testosterone exposure in female rats resulted in increased serum vasopressin and angiotensin II concentrations, leading to the development of hypertension [8], while a chronic blockade of RAS with enalapril abolished age-dependent changes in BP [15], suggesting that the RAS promotes oxidative stress leading to production of vasoconstrictor substances and reduction in nitric oxide availability. In our study, we have not observed any relationship between TT and RAS, but it may be due to small sample size.

Salt-sensitivity of blood pressure has been suggested as a result of the interaction of many genetic and environmental factors [16]. In recent years testosterone-dependent pressure-natriuresis relationship has been highlighted [3, 6, 17, 18]. According to these data, we have shown a positive correlation

Table V. Correlations between testosterone serum level and selected parameters

	Variables	R	P-value
Testosterone [pg/ml]	Age (years)	-0.25	p < 0.03
	BMI [kg/m ²]	-0.05	ns
	Duration of hypertension (months)	0.16	ns
	24 SBP [mm Hg]	0.22	p < 0.05
	24 DBP [mm Hg]	-0.20	ns
	24 MAP [mm Hg]	-0.01	ns
	SBPd [mm Hg]	0.23	p < 0.04
	DBPd [mm Hg]	-0.01	ns
	MAPd [mm Hg]	-0.16	ns
	SBPn [mm Hg]	0.04	ns
	DBPn [mm Hg]	-0.28	p < 0.02
	MAPn [mm Hg]	-0.16	ns
	Sodium in 24h urine collection [mmol/24h]	0.26	p < 0.03
	Potassium in 24h urine collection [mmol/24h]	0.25	p < 0.03
	PRA [ng/ml/h]	-0.02	ns
	Aldosterone [pg/ml]	-0.06	ns
	ARR	-0.21	ns
	LVdMI [g/m ²]	0.26	p < 0.03
	RWT	0.15	ns
	Septal velocity [cm/s]	-0.14	ns
Lateral velocity [cm/s]	-0.06	ns	
LAVI [ml/m ²]	-0.07	ns	
E/e' Ratio	0.01	ns	

R — Spearman rank correlation coefficient; ns — no statistical significance

Table VI. Comparison of selected parameters among women and men groups

	Women (n = 35)	Men (n = 45)	P-value
Age (years)	30.3 ± 7.3	29.5 ± 10.1	ns
BMI [kg/m ²]	28.3 ± 6.0	28.8 ± 6.4	ns
Testosterone [pg/ml]	3.8 ± 3.2	15.5 ± 10.1	p < 0.0001
24 SBP [mm Hg]	122.7 ± 9.9	130.0 ± 10.1	p < 0.05
24 DBP [mm Hg]	77.1 ± 8.5	75.0 ± 8.1	ns
24 MAP [mm Hg]	91.9 ± 8.5	92.4 ± 7.8	ns
SBPd [mm Hg]	127.4 ± 13.1	132.9 ± 10.8	p < 0.005
DBPd [mm Hg]	79.9 ± 8.0	77.9 ± 8.8	ns
MAPd [mm Hg]	94.9 ± 15.3	94.2 ± 10.6	ns
SBPn [mm Hg]	114.8 ± 12.1	115.0 ± 7.7	ns
DBPn [mm Hg]	71.9 ± 13.3	66.1 ± 6.8	p < 0.02
MAPn [mm Hg]	83.6 ± 13.4	82.6 ± 9.9	ns
Dippers	54.3% (19)	76.0% (34)	ns
Non-dippers	45.1 (15)	24.0% (11)	ns
Reverse-dippers	0.9% (1)	0% (0)	ns

24 SBP — 24-hour systolic blood pressure; 24 DBP — 24-hour diastolic blood pressure; 24 MAP — 24-hour mean arterial pressure; SBPd — daytime systolic blood pressure; DBPd — daytime diastolic blood pressure; MAPd — daytime mean arterial pressure; SBPn — nocturnal systolic blood pressure; DBPn — nocturnal diastolic blood pressure; MAPn — nocturnal mean arterial pressure

between TT and sodium excretion in 24-hour urine collection.

Some studies examining the relationship between TT and blood pressure suggest that BP increase is secondary to obesity and insulin resistance [19–21]. However, in contrast to these opinion, other studies demonstrated that independently of food intake and weight gain, hyperandrogenaemia did not exacerbate hypertension in female SHR [22]. Because the majority of our respondents were overweight/ obese, further studies are needed to assess this relationship.

A number of factors have been implicated as the underlying cause of the relation between testosterone and blood pressure, including sex and age as most important ones. Our findings showed that testosterone level was inversely correlated with age. Compared with female, men had significantly higher testosterone level, 24-hour and daytime systolic blood pressure and lower nocturnal diastolic blood pressure. We did not found significant association between TT and altered BP profile after adjusting for age.

The influence of sex hormones on the cardiovascular system at least partially explains the occurrence of sex-dependent epidemiological differences in the incidence of hypertension among men and women. In early human studies performed in men, a step-wise decrease in mean systolic and diastolic BP per increasing quartile of testosterone was shown [14], suggesting a linear relationship between circulating hormone level and BP. However, in the recent study carried out in healthy men aged 20–50 years, changes in BP did not appear to be regulated by testosterone levels [23]. Moreover, in hypogonadal elderly men, long-term testosterone therapy was associated with a significant decrease in systolic and diastolic BP [24]. As showed the findings from the NHANES III study, men generally have a higher pressure than women through middle age [25]. This difference is clear until women reach menopause and the lack of hypotensive effect of hormone replacement therapy indicates oestrogen-independent mechanism [26, 27]. Ziemens *et al.* in the longitudinal women-population-based study demonstrated a positive association between total testosterone and the incidence of hypertension [13]. It also has been suggested that free androgen index might be a robust biomarker of the transition to new onset hypertension and higher BP category in postmenopausal women [28]. The impact of testosterone on blood pressure seems to be confirmed by the fact that women with polycystic ovary syndrome or virilising tumours are frequently diagnosed with hypertension [29–31]. On the other hand, some studies showed no association between

testosterone level and BP in peri- and postmenopausal period [32, 33].

In reference to the current guidelines, the assessment of organ damage, including left ventricular mass index, is important to stratify cardiovascular risk in patients with hypertension [12]. Since the relationship between anabolic steroids abuse and sudden cardiac death was observed, many studies have reported an association between testosterone and ventricular hypertrophy [34]. It has been proven that testosterone affect the cardiomyocytes proliferation and promotes cardiac hypertrophy [35]. Consistently, an inverse association between testosterone concentration and central systolic BP (major determinant of left ventricular hypertrophy [LVH]) was reported [36]. Being in line with the majority of reports [37], the current study showed a positive correlation between TT and left ventricular mass index. Opposite to this findings, Gyllenborg *et al.* has found no association between testosterone levels and LVH [38].

In conclusion, testosterone association with blood pressure profile and left ventricular mass in a young hypertensive population seems to be probable but further analysis is necessary.

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