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Cross-sectional and longitudinal associations between serum testosterone concentrations and hypertension: Results from the Fangchenggang Area Male Health and Examination Survey in China

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ABSTRACT

Background: Low testosterone concentrations have been suggested as a risk factor for hypertension, but their contribution to the development of hypertension is not well studied. We carried out a cohort study based on the results of an earlier cross-sectional investigation. We established the association between testosterone concentrations and hypertension.

Method: Data on 2427 healthy male subjects, aged from 17 to 88 y, were collected for the cross-sectional study. A representative sample of 853 individuals who did not suffer from hypertension at baseline was followed up for 4 y. Differences between the tertiles groups of sex hormones were analyzed, relative risks (RR) were estimated using binary logistic regression model.

Results: In the cross-sectional analysis, the serum total testosterone (TT), free testosterone (FT), and bioavailable testosterone (BT) concentrations of the hypertensive population were lower than those of the non-hypertensive population. Binary logistic regression analysis showed that TT, BT, and FT were inversely associated with hypertension. Moreover, decreasing odds ratio (OR) was observed from the lowest tertile group to the highest tertile group. After multivariate adjustment, the correlation between FT, BT, and hypertension was attenuated. Statistically significant differences remained only in the middle tertile group of TT and in the highest tertile group of TT, FT, and BT. In the longitudinal analysis, the 4-y incidence of hypertension was higher in participants with lower TT than in those with higher TT. Subjects in the middle and highest tertile groups of TT had an RR of 0.35 (0.22–0.57) and 0.30 (0.18–0.50), respectively (P for trend < 0.001). After further adjustments, these associations still remained statistically significant.

Conclusions: Serum TT, FT, and BT concentrations were inversely associated with blood pressure in man, and TT independent of age and body mass index (BMI) influences the development of hypertension. Furthermore, TT can be employed as a risk marker for hypertension in the identification of high-risk individuals.

1. Introduction

Hypertension, a major risk factor for cardiovascular disease (CVD), is a growing public health concern worldwide. In China, the prevalence of hypertension among adults is high [1]. Testosterone plays an important role in males as it regulates reproductive function and lipid and

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protein metabolism. Aside from obesity, hypertension, dyslipidemia, metabolic syndrome, and type 2 diabetes mellitus (T2DM), low testosterone concentrations in men have been suggested to be a novel risk factor for CVD [2,3]. Pietri found that plasma TT is independently and inversely associated with central blood pressure (BP) and wave reflections [4]. The same result was obtained by Svartberg, stating that lower concentrations of testosterone in men are associated with higher BP, left ventricular mass, and left ventricular hypertrophy [5].

Low testosterone concentrations in men have been suggested to be an independent risk factor for hypertension or CVD, but its contribution to hypertension development is not well studied. Prior longitudinal studies have suggested that TT can be used as a potential biomarker for increased CVD risk. Torkler et al. conducted a 5-y prospective cohort study and found that men with TT concentrations in the lowest quartile group had an increased risk of incident hypertension relative to men with higher TT concentrations [6]. Congruently, other studies have shown that low plasma testosterone/low sex hormone-binding globulin (SHBG) concentrations are correlated with or predict the occurrence of metabolic syndrome or atherosclerosis [7,8]. Men with low testosterone are advised to take testosterone replacement therapy (TRT) as an early preventive measure for cardiovascular events. However, whether or not testosterone replacement helps decrease the morbidity rate from CVD is still under controversy. Testosterone affects men's body composition by decreasing visceral fat deposition and increasing adipocytokine and pro-inflammatory cytokine secretion, which are helpful in lowering BP [9,10]. However, many studies suggested that TRT treatment as the sole intervention will not help in decreasing BP. Hoyos et al. reported that 18 weeks of TRT in obese men with severe obstructive sleep apnea decreases arterial stiffness but has no effect on BP [11]. Another study on Asian Indian men with T2DM and hypogonadism also concluded that testosterone treatment exerts a neutral effect on insulin resistance and glycemic control and fails to improve dyslipidemia, control BP, or reduce visceral fat [12]. Furthermore, the protective cardiometabolic effect of long-term TRT is not yet known [13].

2. Materials and methods

2.1. Participants

The participants were recruited from the Fangchenggang Area Male Health and Examination Survey (FAMHES), which was initiated in 2009 in Fangchenggang City, Guangxi, China. We carried out a cohort study based on the results of an earlier cross-sectional investigation (Fig. S1). Briefly, 4303 male participants in the study completed a physical examination at the Medical Centre of Fangchenggang First People's Hospital from September 2009 to December 2009. In 2013, subjects of the cohort study underwent physical examination in the same hospital, wherein the physiological and biochemical indexes of the sample population were measured once again.

Subjects who met the following criteria that might influence BP or whose sex hormone concentrations were not measured will be excluded: (1) currently diagnosed with diabetes mellitus, coronary heart disease, stroke, rheumatoid arthritis, or cancer; (2) taking any kind of medication; (3) with impaired hepatic function (alanine transaminase > 2.0 times the normal upper limit); (4) with impaired renal function (serum creatinine > 178 μmol/l); (5) without sex hormone results. A total of 2427 participants were included in the baseline survey.

We excluded the participants who met the following criteria: (1) diagnosed with baseline hypertension and (2) no communication. 995 participants were selected for the 4-y follow-up cohort study. After 4-y follow-up, we excluded 102 participants due to incompleteness data, eventually, 853 participants were included in cohort study. All subjects provided written informed consents, and the study was approved by the Ethics and Human Subject Committee of Guangxi Medical University.

2.2. Epidemiological survey

Information including demographic characteristics (age, education, etc.), lifestyle (smoking, alcohol consumption, and physical activity), health status, and history of disease and medication was obtained by well-trained physicians using a standard questionnaire during a face-to-face interview. Alcohol consumption was considered positive if the participant drinks one or more alcoholic beverages, including beer, wine, or hard liquor, per week. Current smokers were defined as participants who smoked at least once a day for > 6 months. Physical activity was categorized as either yes (exercising > 60 min per week) or no (exercising < 60 min per week).Weight and height were measured without coat and shoes to the nearest 0.1 kg and 0.1 cm, respectively. BMI was calculated as weight (in kilograms)/height (in square meters). Waist circumference (WC) was measured at the midpoint between the inferior costal margin and the superior border of the iliac crest on the midaxillary line. After resting for > 15 min, BP was measured twice with a mercury sphygmomanometer by well-trained nurses, and the average values were then taken.

2.3. Laboratory measurement

Blood sampling was performed in the morning after a 12 h fast. Serum total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and glucose (GLU) concentrations were measured enzymatically with a Dimension-RxL Chemistry Analyzer (Dade Behring, Newark, DE, USA) in the Department of Clinical Laboratory at the Fangchenggang First People's Hospital. Fasting concentrations of serum total testosterone (TT) were also measured. The interassay coefficient of variation for TT was 3.6%. Bioavailable testosterone (BT) and free testosterone (FT) concentrations were calculated based on the serum concentrations of TT [14].

2.4. Definition of hypertension

Hypertension is defined as having a systolic BP (SBP) of ≥140 mmHg and/or a diastolic BP (DBP) of ≥90 mmHg on more than three measurements. Hypertension was defined twice, once at baseline examination, and the second at the end of the 4-y follow-up period.

2.5. Outcome measurement and comorbidities

The outcome of interest in this study was the development of hypertension. Participants with new-onset hypertension after the 4-y follow-up were regarded as new hypertension patients.

2.6. Statistical analysis

For the cross-sectional analysis, first, spearman partial correlation coefficients was used to assess the proportion between serum testosterone concentrations and age, blood pressure. Second, the baseline data between the hypertensive and non-hypertensive groups were compared using independent samples *t*-test or chi-square test, where suitable. Continuous variables were expressed as mean ± standard deviation, and categorical variables were expressed as number (n) and percentage (%). Third, the sex hormone concentrations (TT, FT, and BT) were divided into 3 groups from the lowest tertiles to the highest tertiles. The SBP and DBP of each group were compared using variance analysis and trend line analysis. Fourth, we estimated the association between sex hormones and hypertension using binary logistic regressions. The OR was calculated to test for the presence of hypertension in the middle and highest tertiles of sex hormone. The lowest tertiles of sex hormone were considered as the reference group. Potential confounders included age, BMI, education, alcohol drinking, physical activity, glucose, cholesterol, triglyceride, and LDL.

For the longitudinal analysis, we used binary logistic regressions to

estimate adjusted RR and 95% confidence intervals (CI) for hypertension. The P for trend value and RRs were calculated for the presence of hypertension in the tertiles of serum sex hormone concentration, with the participants in the lowest tertiles of serum sex hormone concentration considered as the reference group. In the multivariate models, we included variables that might confound the relationship between hypertension and sex hormone concentrations, including age, BMI, education, alcohol drinking, physical activity, glucose, cholesterol, triglyceride, and LDL.

Data processing and statistical analyses were performed with SPSS 17.0. All statistical assessments were 2 sided, and $p < .05$ was considered statistically significant.

3. Results

3.1. Cross-sectional association between sex hormone and hypertension

In 2009, 2427 subjects were recruited for the cross-sectional association study. The average age is 37.6 ± 11.12 y. The prevalence of hypertension was 15.02%. The average TT was 21.72 ± 6.68 ng/ml, and the mean serum FT and BT concentrations were 0.41 ± 0.12 ng/ml, 9.98 ± 2.87 ng/ml, respectively.

The distributions of blood pressure base on testosterone are show in Fig. 1A and Fig. S2. Sreum testosterone was negatively correlated with aging. We found a 0.0835 nmol/l per y reduction in serum TT concentrations ($r = -0.139$, $P = .001$), a 0.0049 nmol/l per y reduction in FT serum concentrations($r = -0.463$, $P < .001$), and a 0.119 nmol/l per y reduction in serum BT concentrations(r = −0.463, $P < .001$).

Fig. 1B and Fig. S3 shows that blood pressure was negatively correlated with serum testosterone. Interestingly, systolic blood pressure decreased at 0.3941 mmHg/1 nmol/l of TT($r = -0.169$, $P < .001$), at 23.715 mmHg/1 nmol/l of FT ($r = -0.175$, $P < .001$), and at 0.3411 mmHg/1 nmol/l of BT($r = -0.176$, $P < .001$). Diastolic blood pressure decrease cross-sectionally at 0.2689 mmHg /1 nmol/l of TT($r = -0.177$, P < .001), at 8.309 mmHg /1 nmol/l of FT($r = -0.089$, P < .001), and at 0.3411 mmHg /1 nmol/l of BT($r = -0.095$, P < .001).

Table 1 shows the baseline characteristics of the study participants in relation to hypertension. Hypertension was diagnosed at the screening visit. Hypertension patients were older (45.38 ± 12.54 vs. 36.43 ± 10.41); had higher BMI (25.39 ± 3.72 vs. 23.01 ± 3.17), WC (86.77 ± 9.48 vs. 79.86 ± 8.88), GLU (5.79 ± 1.53 vs. 5.25 ± 0.96), TC (6.10 ± 1.05 vs. 5.64 ± 1.02), TG (2.14 ± 2.55 vs. 1.46 ± 1.52), and LDL (3.22 ± 0.78 vs. 2.93 ± 0.80); and lower TT (18.90 ± 6.33 vs. 22.14 ± 6.63), FT (0.36 ± 0.10 vs. 0.41 ± 0.12), and BT (8.74 ± 2.42 vs. 10.16 ± 2.89) (all $p < .001$) than controls. Education, alcohol drinking status, and physical activity also differed in the 2 groups ($P < .001$, $P = .031$, $P = .023$, respectively).Smoking status was not different (50.8% vs. 54.0%, P=NS). Generally, age; BMI; WC; BP; and the prevalence of obesity, diabetes,

Table 1
Baseline characteristics of the subjects with or without hypertension in 2009.

	Hypertention(n = 317)	Non-hypertention(n = 2110)	P
Age (y)	45.38 ± 12.54	36.43 ± 10.41	< 0.001
SBP (mmHg)	145 ± 14	114 ± 11	< 0.001
DBP (mmHg)	92 ± 10	75 ± 8	< 0.001
Height (cm)	167.75 ± 5.40	168.09 ± 5.60	NS
Weight (Kg)	71.57 ± 11.90	65.08 ± 9.96	< 0.001
BMI (Kg/m^2)	25.39 ± 3.72	23.01 ± 3.17	< 0.001
WC (cm)	86.77 ± 9.48	79.86 ± 8.88	< 0.001
GLU(mmol/l)	5.79 ± 1.53	5.25 ± 0.96	< 0.001
TC(mmol/l)	6.10 ± 1.05	5.64 ± 1.02	< 0.001
TG(mmol/l)	2.14 ± 2.55	1.46 ± 1.52	< 0.001
HDL(mmol/l)	1.41 ± 0.42	1.41 ± 0.32	NS
LDL(mmol/l)	3.22 ± 0.78	2.93 ± 0.80	< 0.001
TT(nmol/l)	18.90 ± 6.33	22.14 ± 6.63	< 0.001
FT(nmol/l)	0.36 ± 0.10	0.41 ± 0.12	< 0.001
BT(nmol/l)	8.74 ± 2.42	10.16 ± 2.89	< 0.001
Education			< 0.001
Primer	23(7.3%)	54(2.6%)	
Senior	72(22.7%)	377(17.9%)	
Higher	222(70.0%)	1676(79.5%)	
Smoking status			NS
Yes	161(50.8%)	1139(54.0%)	
No	156(49.2%)	971(46.0%)	
Alcohol drinking			0.031
Yes	259(81.7%)	1820(86.3%)	
No	58(18.3%)	290(13.7%)	
Physical acting			0.023
Yes	127(40.2%)	708(33.7%)	
No	189(59.8%)	1394(66.3%)	

Abbreviation: WC, waist circumference; TT, testosterone; FT, free testosterone; BT, bioavailable testosterone. Continuous variables were expressed as the mean ± SD, and categorical variables were expressed as number (n) and percentage (%).

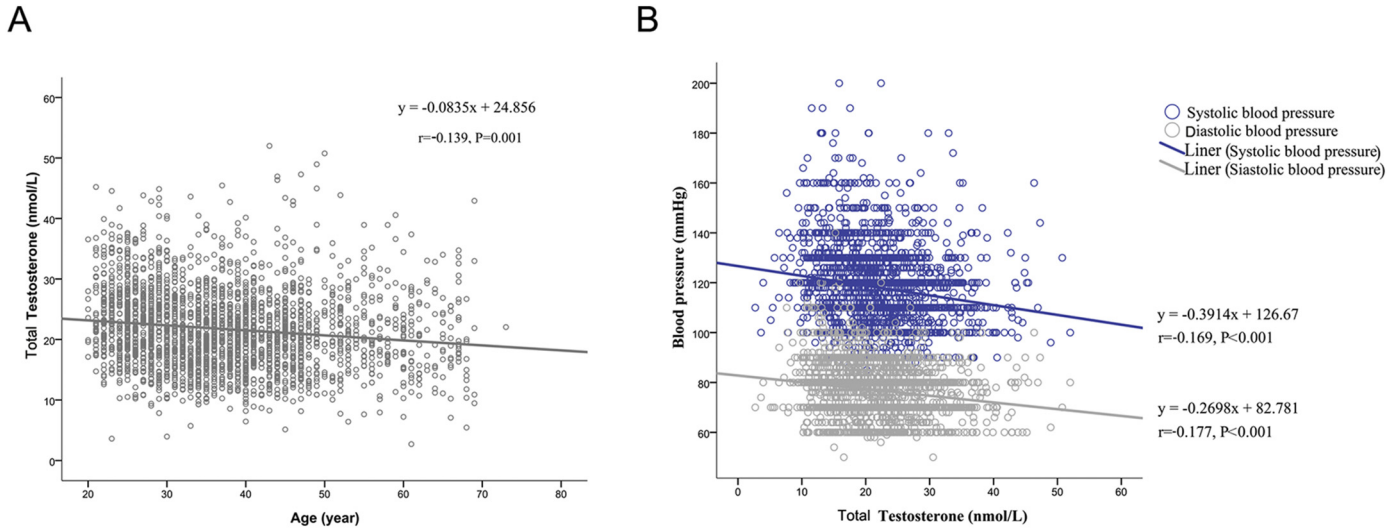

Fig. 1. Spearman partial correlation between serum testosterone levels and age, blood pressure. A. The relationship between Serum total testosterone and age. B. The relationship between blood pressure and serum total testosterone.

Table 2
The comparisons of blood pressure at different testosterone levels.

	Numbers	SBP(mmHg)	DBP(mmHg)
TT(nmol/l)			
< 18.44	804	122 ± 17	79 ± 11
18.44–23.99	813	117 ± 15	76 ± 9
≥23.99	810	115 ± 14	75 ± 9
P for trend		< 0.001	< 0.001
FT(nmol/l)			
< 0.352	810	121 ± 18	78 ± 11
0.352–0.444	809	118 ± 14	77 ± 10
≥0.444	808	114 ± 13	75 ± 9
P for trend		< 0.001	0.001
BT(nmol/l)			
< 8.62	810	121 ± 18	78 ± 11
8.62–10.87	807	118 ± 14	78 ± 10
≥10.87	810	114 ± 13	75 ± 9
P for trend		< 0.001	< 0.001

Abbreviation: TT, testosterone; FT, free testosterone; BT, bioavailable testosterone. Blood pressure were expressed as the mean ± standard deviation(SD).

and dyslipidemia were all significantly higher in hypertensive patients than in controls. By contrast, the concentrations of TT, FT, and BT were markedly lower.

Table 2 shows the comparisons of SBP and DBP at different sex hormone concentrations. Sex hormone concentrations were divided into 3 groups from the lowest tertiles to the highest tertiles. Compared with those in the lowest tertile group, the SBP and DBP in the middle and high tertile groups were significantly lower. They both decreased with increasing TT concentrations (P for trend < 0.001). A similarly consistent trend was found in FT (P for trend < 0.001 or = 0.001) and BT (all P for trend < 0.001).

Table 3 shows the relationships between sex hormone concentrations and the risk of hypertension. Using the lowest tertiles as reference, decreasing OR was observed from the lowest group to the highest group. Subjects in the middle and highest tertiles had an OR of 0.43 (0.32–0.56) and 0.27 (0.19–0.37) for TT, 0.59 (0.45–0.77) and 0.26 (0.18–0.36) for FT, and 0.58 (0.45–0.76) and 0.25 (0.18–0.36) for BT, respectively (all P for trend < 0.001). However, after adjusting for age, BMI, education, alcohol drinking, physical activity, glucose, cholesterol, TG, and LDL, the correlation between TT and hypertension remained, but that between FT, BT, and hypertension became weak.

Table 3
The relationships between testosterone levels and the risk of hypertension in 2009.

	Unadjusted model	Adjusted model
	OR (95%CI)	OR (95%CI)
TT(nmol/l)		
< 18.44	1.00	1.00
18.44–23.99	0.43(0.32–0.56)	0.64(0.47–0.88)
≥23.99	0.27(0.19–0.37)	0.58(0.40–0.83)
P for trend	< 0.001	0.001
FT(nmol/l)		
< 0.352	1.00	1.00
0.352–0.444	0.59(0.45–0.77)	0.96(0.72–1.30)
≥0.444	0.26(0.18–0.36)	0.67(0.46–0.98)
P for trend	< 0.001	NS
BT(nmol/l)		
< 8.62	1.00	1.00
8.62–10.87	0.58(0.45–0.76)	0.95(0.71–1.28)
≥10.87	0.25(0.18–0.36)	0.66(0.45–0.97)
P for trend	< 0.001	NS

Abbreviation: TT, testosterone; FT, free testosterone; BT, bioavailable testosterone. ORs were adjusted by age, BMI, education, alcohol drinking, physical acting, glucose, cholesterol, triglyceride, and low density lipoprotein.

3.2. Longitudinal association between tertile concentrations of sex hormone and hypertension

Table 4 shows the RRs and 95% CIs for hypertension according to the testosterone categories. The incidence of hypertension decreased with increasing TT. Using the lowest tertiles as reference, in an unadjusted model, subjects in the middle tertile had an RR of 0.37 (0.23–0.59) and those in the highest tertile had a RR of 0.31 (0.19–0.51) (P for trend < 0.001). These associations were attenuated but still remained statistically significant, even after further adjustments for covariates in models 1 (age and BMI), 2 (age, BMI, glucose, cholesterol, TG, and LDL), and 3 (age, BMI, education, alcohol drinking, physical activity, glucose, cholesterol, TG, and LDL).

The same tendency was found in FT and BT. Compared with the subjects with the lowest concentration, those in the middle and highest tertiles of FT had an RR of 1.01 (0.65–1.57) and 0.59 (0.36–0.98), respectively (P for trend =0.051). Subjects in the middle and highest tertiles of BT had an RR of 1.02 (0.65–1.58) and 0.59 (0.36–0.98), respectively (P for trend = NS). However, the statistical differences after adjustments for covariates were not determined.

4. Discussion

Overall, the present study showed that men with hypertension had lower TT, FT, and BT concentrations compared with controls. Furthermore, TT, FT, and BT were inversely correlated with SBP and DBP. The 4-y incidence of hypertension was lower in participants with higher TT, and men with low TT concentrations were identified as high-risk individuals with regard to the 4-y hypertension risk.

Several epidemiological studies suggested that low testosterone concentrations may be related to higher BP. Johan et al. reported that men with categorical hypertension had low concentrations of TT and FT before and after adjusting for BMI [5]. Our study confirmed that testosterone, the most important male sex hormone, had a significant effect on male BP. In the cross-sectional analysis, we found that after adjusting age, BMI, education, alcohol drinking, physical activity, glucose, cholesterol, TG, and LDL, the correlation between TT and hypertension remained. However, the correlation between FT, BT, and hypertension weakened. One possible explanation is that the association of low testosterone concentrations with BP might be mediated by obesity. BMI and WC are proportionate to the index of visceral fat. Visceral fat accumulation is linked to testosterone [15], so the association between TT and hypertension will be reduced after adjusting for BMI or WC [5,16,17]. A second possible explanation is that serum testosterone concentrations decline with aging, TT and FT decrease disproportionately, and FT concentrations decline more rapidly than TT concentrations [7]. Therefore, the relationship between FT, BT, and hypertension might be weakened after adjusting for age. A third possible explanation is that the relationship between BT and hypertension may be partially disturbed by serum SHBG. In addition to being a carrier for sex hormones, a numbers of studies have shown that SHBG exhibits biological activity. Reduced concentrations of SHBG are significant predictors of metabolic syndrome (MetS), non-alcoholic fatty liver disease, and T2DM independent of testosterone [2,18–20].

In the longitudinal analysis, we found that the 4-y incidence of hypertension was higher in participants with serum TT lower than 18.5 nmol/l. As the serum concentration of TT is a strong predictor for developing hypertension, clarifying the association between testosterone and increased risk of hypertension is important. The European guidelines define erectile dysfunction (ED) or testosterone define (TD) as TT ≤ 8 nmol/l, and the “borderline” testosterone concentration is 8–12 nmol/l; TRT is recommended if TT ≤ 8 nmol/l [21,22]. This threshold was verified by many studies [23]. However, some researchers believed that low endogenous testosterone, even higher than the threshold for TD (8.0 nmol/l), is associated with hypertension or CVD risk [24,25]. Martinez also reported that several CVD risk factors

Table 4
Longitudinal association between testosterone levels and the risk of hypertension.

Testosterone levels	No. At risk	Hypertension cases	Unadjusted	Adjusted model
			RR (95%CI)	RR (95%CI)
TT(nmol/l)				
< 18.44	252	62	1.00	1.00
18.44–23.99	299	32	0.37(0.23–0.59)	0.47(0.28–0.78)
≥23.99	302	28	0.31(0.19–0.51)	0.39(0.22–0.69)
P for trend			< 0.001	0.001
FT(nmol/l)				
< 0.352	279	45	1.00	1.00
0.352–0.444	301	49	1.01(0.65–1.57)	1.62(0.96–2.74)
≥0.444	273	28	0.59(0.36–0.98)	1.26 (0.68–2.33)
P for trend			NS	NS
BT(nmol/l)				
< 8.62	279	45	1.00	1.00
8.62–10.87	300	49	1.02(0.65–1.58)	1.62(0.96–2.74)
≥10.87	274	28	0.59(0.36–0.98)	1.26 (0.68–2.34)
P for trend			0.049	NS

Abbreviation: TT, testosterone; FT, free testosterone; BT, bioavailable testosterone. RRs were adjusted by age, BMI, education, alcohol drinking, physical acting, glucose, cholesterol, triglyceride, and low density lipoprotein.

are commonly observed not only in men with low testosterone concentrations, as described by the European guidelines, but also in men having so-called "borderline" T concentrations (8–12 nmol/l) [24]. Previously, we reported a strong association between TT and MetS. We found that in the lowest tertile group of serum TT concentrations, the TT cutoff line was much higher (TT < 17.05 nmol/l) than the threshold for TT 8 nmol/l [26]. According to these data, we suggest that the hypertension risk of men with low testosterone concentrations could be significantly higher for testosterone concentrations below a threshold of 12 nmol/l or even more in Chinese men.

In the body, testosterone circulates in three forms: tightly bound to SHBG (60%), loosely bound to albumin (38%), and in a free form (2%). FT is believed to be the metabolically active fraction [14]. However, directly detecting FT is difficult. Normally calculated FT is used to represent serum FT concentrations. Therefore, it is not known which among the three, TT, FT, and BT, is the best biomarker that represents the associations between testosterone and hypertension. In our study, the cross-sectional logistic regression models revealed a significant inverse association between TT, FT, and BT with prevalent hypertension. After further adjustment, significant differences remained only between TT and hypertension. In the longitudinal analyses, lower baseline TT was associated with incident hypertension. Therefore, we suggested that TT is a better risk marker for hypertension than FT or BT and can be employed in the identification of high-risk hypertensive individuals.

This study had inevitable limitations. First, only two health examination information in 2009 and 2013 were collected. Dynamic monitoring of physiological change every year may have provided deeper insight on the contribution of testosterone in the development of hypertension. Second, although two physical examinations (2009, 2013) have been performed in this cohort, sex hormone concentrations were detected only one time at baseline in 2009. Third, 4 y was a relatively short follow-up period. Fourth, our study participants were not a random sample, they were participants from the FAMHES.

5. Conclusion

Serum TT, FT, and BT concentrations were inversely associated with BP in men. TT, independent of age and BMI, influenced the development of hypertension. It is a risk marker that is beneficial for the identification of high-risk hypertensive individuals. Our results reinforced the need to address the causal relationship and pathophysiological interactions between testosterone concentrations and hypertension.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cca.2018.08.027.

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