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HIGH NORMOTENSION IS ASSOCIATED WITH METABOLIC SYNDROME BUT NOT NON-FATAL CARDIOVASCULAR EVENTS

Medicine

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ABSTRACT

Introduction: Due to the blood pressure was one of the diagnosis criteria in MetS, blood pressure was increased with aging. Whether the increased blood pressure in normotensive range is still associated with MetS and more important, cardiovascular disease, we conducted a 4-year longitudinal observation study to elucidate these association.

Methods: a total 9,133 subjects were qualified for analysis. We further grouped these subjects into SBP1 to SBP3 and DBP1 and DBP3. SBP1 was SPB < 99 mmHg, SBP2 was SPB >100, < 109 mmHg, SBP3 was SPB >110, < 119 mmHg. DBP1 was DPB < 59 mmHg, DBP2 was DPB >60, < 69 mmHg, DBP3 was DPB >70, < 79 mmHg.

Results: After 4 years of follow-up, SBP3 group still had higher risk of developing future MetS but not future non-fatal cardiovascular diseases. However, SBP3 group in female fail to show significant in future MetS. In addition, both SPB3 group and DPB3 group fail to show significant in developing future non-fatal cardiovascular diseases.Kaplan-Meier estimates showed both SPB and DBP groups showed significant difference in developing future MetS but not in developing future non-fatal cardiovascular diseases.

Conclusion: In conclusion, high normotensive bloop pressure is still a risk for having MetS in the future but not non-fatal cardiovascular diseases. DBP looks more sensitive than SBP in the future events development in the elderly.

KEYWORDS

Blood pressure, metabolic syndrome, type 2 diabetes, cardiovascular disease

INTRODUCTION

The high prevalence of metabolic syndrome (MetS) is not unique to the United States and Europe. In Asian Indians, the prevalence of MetS is 5% in rural populations but increases to greater than one-third of the population in urban settings [1]. Moreover, The prevalence of MetS also increases with aging [2]. From Cardiovascular Health Study (CHS) in the United States, in adults older than 65 years, there was an overall prevalence of MetS of 35% [3]. Obesity, hypertension, dyslipidemia, and prediabetes often clustered together with a high predictability for the future occurrence of cardiovascular diseases and diabetes are regarded as the components of MetS. By definition, MetS is not a disease, but is a clustering of individual risk factors for disease, drawing the attention of the clinician to the probable coexistence of multiple cardiometabolic risk factors in patients when one of the components is found [4]. Therefore, a diagnosis of MetS could be expected to predict risk. The goal is to target the different components of MetS with lifestyle and pharmacologic therapies to prevent disease, particularly cardiovascular diseases and diabetes [5]. Due to the blood pressure was one of the diagnosis criteria in MetS, blood pressure was increased with aging. Whether the increased blood pressure in normotensive range is still associated with MetS and more important, cardiovascular disease, we conducted a 4-year longitudinal observation study to elucidate these association.

METHODS

Study participants

We enrolled subjects who underwent routine medical check-ups at tri-service medical center. It is the Informed consents were collected from all anonymous participants and this study protocol was approved by the institutional review board. A total of 21,318 subjects between 65 and 80 years old were enrolled from January 2014 to December 2016. The inclusion criteria of age equal to and over 65 years old was based on the WHO definition. We excluded subjects with a history of diabetes, hypertension, abnormal lipid profile, CVD and those taking medications for these diseases at baseline. We also excluded the study subjects with the follow-up periods lesser than 4 years. Moreover, subjects with BP ≧ 120/80 mmHg were also excluded. At last, 9133 subjects were qualified for further analysis. We further grouped these subjects into SBP1 to SBP3 and DBP1 and DBP3. SBP1 was SPB < 99 mmHg, SBP2 was SPB >100, < 109 mmHg, SBP3 was SPB >110, < 119 mmHg. DBP1 was DPB < 59 mmHg, DBP2 was DPB >60, < 69 mmHg, DBP3 was DPB >70, < 79 mmHg.

Anthropometric and laboratory data

The health examinations consisted of a medical history taking including the subject's current medication, a complete physical examination, blood pressure, anthropometric measurements and fasting plasma blood samples. Trained senior nursing staffs took all the measurements. SBP and DBP were measured by nursing staf using mercury sphygmomanometers with appropriate sized cuffs on the right arm of the participants, who had rested for at least 5 min in a sitting position. Two measurements were taken more than 1 min apart and the average was recorded.

Blood samples were drawn after a 10-h fast and plasma derived from it within 1 h and store at −30°C. Te plasma was then measured for fasting plasma glucose (FPG) and lipid profiles. Te glucose oxidase method (YSI 203 glucose analyzer, Scientific Division, Yellow Spring Instruments, Yellow Spring, OH, USA) was used to check the FPG. Total cholesterol (TC) and triglyceride (TG) were tested using the dry, multilayer analytical slide method in the Fuji Dri-Chem 3000 analyzer (Fuji Photo Film, Minato-Ku, Tokyo, Japan). An enzymatic cholesterol assay following dextran sulfate precipitation was used to examine serum high-density lipoprotein-cholesterol (HDL-C) and low-density lipoprotein-cholesterol (LDL-C) concentration.

STATISTICALANALYSIS

SPSS version 25.0 software (IBM, Somers, NY, USA) was used to perform all the statistical analyses in 2012. To compare the difference between the three groups, one-way analysis of variance (ANOVA) test was used with Bonferroni test as the post-hoc test. Logistic regression analysis was performed to examine odds ratios (ORs) for having each abnormal MetS component or MetS itself among the three groups at baseline. For the follow-up data, Hazard ratio and log rank test with Kaplan-Meier plots were analyzed. All statistical tests were two-sided and $p < 0.05$ was statistically significant.

RESULTS

There were 4,634 male and 4,499 female enrolled in the current study. All subjects were grouped into SBP1 to SBP and DBP1 and DBP3 according to the SPB and DBP levels (Table 1).

Table 1. Clinical Characteristics of the Study Subjects in (a) systolic blood pressure subgroup and (b) diastolic blood pressure subgroup at baseline.

(a)

	SBP 1			SBP 2			SBP 3		
Male									
	460			1579			2595		
Age, year	64.5	±	4.9	64.6	±	5.2	65.1	±	5.4[a,b]
BMI, kg/m^2	22.4	±	2.9	22.8	±	3.0[a]	23.3	±	2.9[a,b]
WC, cm	80.9	±	8.6	82.0	±	8.8[a]	83.2	±	8.4[a,b]
SBP, mm Hg	95.5	±	2.9	105.1	±	2.8[a]	114.7	±	2.9[a,b]

DBP, mm Hg	61.0	±	6.3	65.0	±	6.0[a]	68.3	±	6.0[a,b]
FPG, mg/dL	105.1	±	34.0	105.7	±	31.9	106.2	±	28.6
TC, mg/dL	192.0	±	35.3	196.9	±	36.0[a]	197.8	±	36.8[a]
HDL-C, mg/dL	50.5	±	14.8	51.3	±	14.7	50.2	±	13.7[b]
LDL-C, mg/dL	119.9	±	31.3	123.1	±	31.5	123.4	±	33.5
TG, mg/dL	108.3	±	57.9	112.7	±	60.8	120.0	±	63.8[a,b]
Female									
	479			1466			2554		
Age, year	62.4	±	3.5	63.4	±	4.2[a]	63.8	±	4.3[a,b]
BMI, kg/m^2	22.5	±	3.0	23.0	±	3.1[a]	23.5	±	3.1[a,b]
WC, cm	73.7	±	7.0	75.5	±	7.7[a]	76.6	±	8.0[a,b]
SBP, mm Hg	95.3	±	2.9	105.0	±	2.9[a]	114.8	±	2.9[a,b]
DBP, mm Hg	58.9	±	6.0	62.6	±	6.2[a]	66.2	±	6.0[a,b]
FPG, mg/dL	101.8	±	23.7	102.7	±	27.2	105.0	±	28.6[b]
TC, mg/dL	205.4	±	34.8	208.3	±	36.8	212.0	±	37.4[a,b]
HDL-C, mg/dL	61.0	±	16.1	60.4	±	16.0	59.9	±	15.9
LDL-C, mg/dL	123.1	±	31.5	124.9	±	33.6	127.9	±	34.1[a,b]
TG, mg/dL	106.2	±	54.0	114.6	±	58.1[a]	121.1	±	71.5[a,b]

Data are shown as mean ± SD.
[a]$P<0.05$ against SBP 1; [b]$P<0.05$ against SBP 2.
Abbreviations: BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; SBP, systolic blood pressure.

(b)

	DBP 1			DBP 2			DBP 3		
Male									
	687			2375			1610		
Age, year	66.6	±	6.3	65.0	±	5.2[a]	63.9	±	4.6[a,b]
BMI, kg/m^2	22.4	±	3.0	22.9	±	2.8[a]	23.5	±	3.0[a,b]
WC, cm	81.2	±	9.0	82.1	±	8.5[a]	83.7	±	8.6[a,b]
SBP, mm Hg	103.7	±	8.7	108.8	±	7.0[a]	112.3	±	5.7[a,b]
DBP, mm Hg	55.9	±	2.7	64.8	±	2.8[a]	73.3	±	2.6[a,b]
FPG, mg/dL	109.7	±	42.6	105.5	±	28.4[a]	104.7	±	26.1[a]
TC, mg/dL	191.4	±	37.1	196.2	±	36.7[a]	200.3	±	35.3[a,b]
HDL-C, mg/dL	50.1	±	14.3	50.8	±	14.1	50.5	±	14.2
LDL-C, mg/dL	119.2	±	32.5	122.7	±	32.5[a]	124.9	±	32.6[a]
TG, mg/dL	110.4	±	61.8	113.5	±	60.4	122.3	±	64.5[a,b]
Female									
	1051			2447			1028		
Age, year	64.0	±	4.7	63.4	±	4.1[a]	63.2	±	3.9[a]
BMI, kg/m^2	22.7	±	3.0	23.3	±	3.1[a]	23.7	±	3.2[a,b]
WC, cm	74.8	±	7.3	75.9	±	7.9[a]	77.1	±	8.2[a,b]
SBP, mm Hg	104.8	±	8.2	109.9	±	7.0[a]	112.7	±	5.7[a,b]
DBP, mm Hg	55.7	±	2.6	64.2	±	2.8[a]	73.1	±	2.6[a,b]
FPG, mg/dL	104.5	±	27.1	103.9	±	28.7	103.2	±	25.2
TC, mg/dL	209.3	±	37.4	210.2	±	36.7	211.1	±	37.3
HDL-C, mg/dL	61.4	±	16.2	60.0	±	15.8[a]	59.5	±	16.2[a]
LDL-C, mg/dL	126.0	±	34.5	126.7	±	33.3	126.3	±	33.8
TG, mg/dL	109.6	±	56.5	117.2	±	60.5[a]	125.6	±	83.1[a,b]

Data are shown as mean ± SD.
[a]$P<0.05$ against DBP 1; [b]$P<0.05$ against DBP 2.
Abbreviations: BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; DBP, diastolic blood pressure.

The mean SBP in each group were 95.5±2.9, 105.1±2.8, 114.7±2.9 in male and 95.3±2.9, 105.0±2.9, 114.8±2.9 in female, accordingly. The mean DBP in each group were 61.0±6.3, 65.0±6.0, 68.3±6.0 in male and 58.9±6.0, 62.6±6.2, 66.2±6.0 in female, accordingly. At baseline, the SPB3 group or DBP3 group had highest risk for having MetS or its components (Table 2).

Table 2. Odds ratios for having metabolic syndrome and each abnormal component in (a) systolic and (b) diastolic blood pressure groups at baseline.

(a)

		SBP 1	SBP 2	SBP 3
Male				
WC ≥ 90 cm	OR	Ref.	1.229 (0.930 – 1.623)	1.468 (1.126 – 1.915)
	p	---	0.148	0.005
FPG ≥ 100 mg/dL	OR	Ref.	0.997 (0.809 – 1.229)	1.319 (1.080 – 1.609)
	p	---	0.979	0.007
HDL-C < 40 mg/dL	OR	Ref.	1.165 (0.888 – 1.528)	1.517 (1.172 – 1.961)
	p	---	0.270	0.002
TG ≥ 150 mg/dL	OR	Ref.	0.968 (0.755 – 1.241)	0.979 (0.772 – 1.241)
	p	---	0.796	• 0.859
Metabolic syndrome	OR	Ref.	1.136 (0.792 – 1.629)	1.510 (1.074 – 2.122)
	p	---	0.487	0.018
Female				
WC ≥ 80 cm	OR	Ref.	1.674 (1.290 – 2.172)	2.142 (1.672 – 2.744)
	p	---	< 0.001	< 0.001
FPG ≥ 100 mg/dL	OR	Ref.	1.105 (0.894 – 1.366)	1.371 (1.122 – 1.675)
	p	---	0.354	0.002
HDL-C < 50 mg/dL	OR	Ref.	1.435 (1.091 – 1.886)	1.699 (1.310 – 2.203)
	p	---	0.010	< 0.001
TG ≥ 150 mg/dL	OR	Ref.	1.101 (0.865 – 1.400)	1.240 (0.988 – 1.557)
	p	---	0.436	0.064
Metabolic syndrome	OR	Ref.	1.658 (1.165 – 2.362)	1.996 (1.424 – 2.796)
	p	---	0.005	< 0.001

Abbreviations: OR, odds ratio; WC, waist circumference; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein-cholesterol; TG, triglycerides; Ref, reference; SBP, systolic blood pressure.

(b)

		DBP 1	DBP 2	DBP 3
Male				
WC ≥ 90 cm	OR	Ref.	1.176 (0.936 – 1.479)	1.751 (1.387 – 2.211)
	p	—	0.165	< 0.001
FPG ≥ 100 mg/dL	OR	Ref.	0.980 (0.827 – 1.161)	1.024 (0.857 – 1.225)
	p	---	0.812	0.793
HDL-C < 40 mg/dL	OR	Ref.	1.205 (0.969 – 1.498)	1.496 (1.195 – 1.873)
	p	---	0.094	< 0.001
TG ≥ 150 mg/dL	OR	Ref.	0.881 (0.721 – 1.077)	0.912 (0.738 – 1.126)
	p	---	0.215	0.392
Metabolic syndrome	OR	Ref.	1.018 (0.772 – 1.343)	1.274 (0.959 – 1.693)
	p	---	0.897	0.095
Female				
WC ≥ 80 cm	OR	Ref.	1.406 (1.187 – 1.665)	1.837 (1.514 – 2.230)
	p	---	< 0.001	< 0.001
FPG ≥ 100 mg/dL	OR	Ref.	0.952 (0.823 – 1.102)	0.910 (0.765 – 1.082)
	p	---	0.512	0.286
HDL-C < 50 mg/dL	OR	Ref.	1.244 (1.038 – 1.491)	1.556 (1.265 – 1.914)
	p	---	0.018	< 0.001
TG ≥ 150 mg/dL	OR	Ref.	1.155 (0.977 – 1.366)	1.312 (1.080 – 1.594)
	p	---	0.091	0.006
Metabolic syndrome	OR	Ref.	1.315 (1.052 – 1.644)	1.706 (1.328 – 2.191)
	p	---	0.016	< 0.001

Abbreviations: OR, odds ratio; WC, waist circumference; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein-cholesterol; TG, triglycerides; Ref, reference; DBP, diastolic blood pressure.

However, SBP3 group in both genders fail to show significant in TG, and DBP3 group in both genders fail to show significant in FPG. Moreover, DBP3 group in male fail to show significant in TG and MetS itself. After 4 years of follow-up, SBP3 group still had higher risk of developing future MetS and future non-fatal cardiovascular diseases (Table 3).

Table 3. Hazard ratios for having metabolic syndrome and non-fatal cardiovascular event in (a) systolic and (b) diastolic blood pressure groups in the follow up periods.

(a)

		SBP	SBP 2	SBP 3
Male				

Metabolic syndrome	OR	Ref.	1.353	(0.789	–	2.322)	1.882	(1.123	–	3.156)
	p	---	0.272				0.016			
Cardiovascular event	OR	Ref.	1.616	(0.623	–	4.190)	1.989	(0.791	–	5.001)
	p	---	0.324				0.144			
Female										
Metabolic syndrome	OR	Ref.	0.924	(0.584	–	1.461)	1.493	(0.983	–	2.269)
	p	---	0.735				0.060			
Cardiovascular event	OR	Ref.	0.916	(0.385	–	2.180)	1.245	(0.559	–	2.772)
	p	---	0.843				0.591			

Abbreviations: OR, odds ratio; SBP, systolic blood pressure.

(b)

		DBP 1	DBP 2				DBP 3			
Male										
Metabolic syndrome	OR	Ref.	1.565	(0.992	–	2.469)	1.891	(1.192	–	3.000)
	p	---	0.054	0.007						
Cardiovascular event	OR	Ref.	1.119	(0.575	–	2.180)	1.119	(0.560	–	2.237)
	p	—	0.740	0.751						
Female										
Metabolic syndrome	OR	Ref.	1.463	(1.031	–	2.078)	1.827	(1.246	–	2.680)
	p	---	0.033	0.002						
Cardiovascular event	OR	Ref.	0.995	(0.540	–	1.832)	1.023	(0.499	–	2.097)
	p	---	0.987				0.951			

Abbreviations: OR, odds ratio; DBP, diastolic blood pressure.

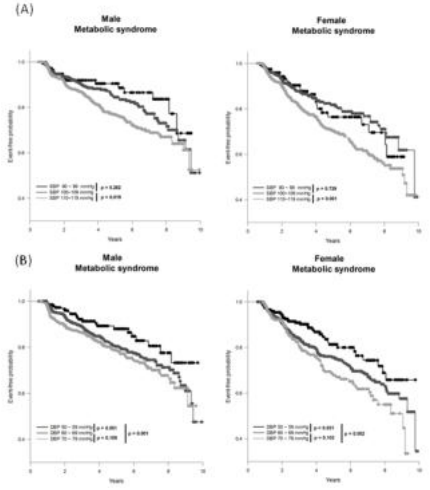

Figure 1. Kaplan-Meier estimates of metabolic syndrome in different normal systolic and diastolic blood pressure levels

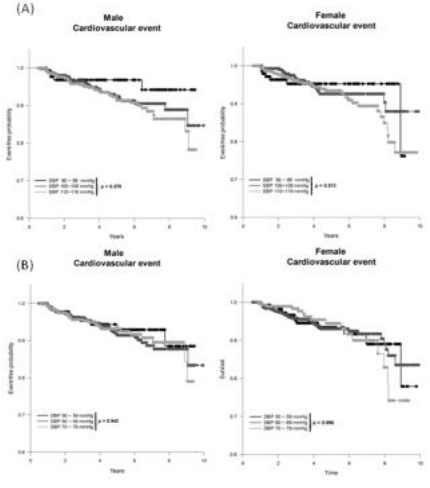

Figure 2. Kaplan-Meier estimates of non-fatal cardiovascular event in different normal systolic and diastolic blood pressure levels

However, SBP3 group in female fail to show significant in future MetS. In addition, both SPB3 group and DPB3 group fail to show significant in developing future non-fatal cardiovascular diseases. In figure 1 and 2, Kaplan-Meier estimates of MetS and non-fatal cardiovascular diseases in different SBP and DBP groups. Similar to the Hazard ratio results, both SPB and DBP groups showed significant difference in developing future MetS but not in developing future non-fatal cardiovascular diseases.

DISCUSSIONS

It's still interesting to know if the harmful effects of blood pressure extend to people with normal blood pressure [6] Within the normal blood pressure range, not only body weight, but age is also well known to have a positive correlation with SBP [7]. Age was found to be associated with increased SBP previously [8-10] One of the possible causes of this process is the increasing of the aortic stiffness, which is related to increased collagen with crosslinking and degradation of elastin fibers [11]. Impaired glucose metabolism is associated with the progression of atherosclerosis [12-14]. Conversely, a sustained increase in blood pressure is associated with an increased risk of developing new diabetes [15]. A population-based observational study reported a continuous and graded relationship of blood pressure and cardiovascular disease and mortality [16]. A systolic BP < 120 mm Hg is considered ideal, with each 10 mm Hg increase in BP above this being accompanied by a 10% greater risk of cardiovascular events and mortality [17].

The accepted unified hypothesis that explains the pathophysiology of MetS is insulin resistance. Insulin resistance has traditionally been defined with a glucocentric view—ie, when a defect in insulin action results in fasting hyperinsulinaemia to maintain euglycaemia. However, there are conditions in hyperinsulinemia, ont only in postprandial, but also in fasting status. The main cause of insulin resistance is excess circulating fatty acids. [18] This effedt was shoen in high waist circumferential subjects that seems to contribute to this process. The visceral fat component of abdominal obesity leads to not only insulin resistance but also the release of nonesterified free fatty acids from adipose tissue. Thus, lipids accumulate in other sites such as liver and muscle, further predisposing to insulin resistance and dyslipidemia [19].

The clinical significance of 'white-coat' hypertension (WCHT) is the condition in which blood pressure is elevated in the clinic environment but normal in daily life, is still controversial [20-23]. Conversely, 'masked' hypertension (MHT) is a condition in which blood pressure is normal in the clinic environment but elevated in daily life [22, 24] The risk of developing diabetes and impairing fasting blood glucose in WCHT and MHT is independent of the use of antihypertensive drugs. Quantitatively, similar to that of sustained hypertensive individuals, that is, those in whom both in and out-of-office blood pressure are greater than normal, the increase being in all three abnormal BP states not marginally but markedly (i.e. more than 2–3 times) more pronounced than that of truly normotensive individuals. This is new evidence supporting the conclusion that WCHT and MHT are medically harmless. [25] Indeed, because in diabetes, the rate of cardiovascular events is linked to the duration of disease [26, 27], over the long term, the prognostic impact of WCHT and MHT could be more adverse than what has been reported by studies of only a few years duration [28-30].

In conclusion, high normotensive bloop pressure is still a risk for having MetS in the future but not non-fatal cardiovascular diseases. DBP looks more sensitive than SBP in the future events development in the elderly.

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