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Increased incidence of metabolic syndrome in older men with high normotension

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***Introduction*: Hypertension and prehypertension are correlated with future cardiovascular disease (CVD) and diabetes. Whether these harmful effects of the blood pressure (BP) could be found in normotensive is of interest. *Methods*: In this cross-sectional study, totally 2388 normotensive older men aged 65–80 years undergoing routine health examinations were enrolled. To eliminate the influence of age on BP, subjects were initially grouped in each age stratum. Then in each age-stratum, subjects were further grouped into low, middle and high-tertile systolic BP (SBP) subgroups. Finally, all the low-tertile subgroups in each age stratum were gathered to form Group-1. Similarly, Group-2 (middle-tertile) and Group-3 (high-tertile) were also created. Metabolic syndrome (MetS) was regarded as having risks for future CVD and diabetes. *Results*: Age, waist circumstance (WC), fasting plasma glucose (FPG) and log triglyceride (TG) were independently and significantly correlated with SBP by multiple linear regression analysis. On the other hand, logistic regression showed that Group-3 had significant higher odds ratios (ORs) for having abnormal WC, FPG and TG. In addition, Group-3 presented a 1.55–fold OR ($p < 0.001$) for having MetS than Group-1. *Conclusions*: In normotensive older men, the risk for having MetS was significantly associated with higher SBP. Primary prevention of hypertension should be stressed.**

Keywords: Metabolic syndrome, normotension, older men, preventive geriatrics

Introduction

The clustering of hypertension, obesity, dyslipidemia and hyperglycemia has been noted for more than two decades. In 1998, the World Health Organization (WHO) recognized the rapidly increasing incidences of cardiovascular diseases (CVD) and diabetes [1]. The term, metabolic syndrome (MetS), was then first proposed to denote the clustering of these 4 components. Since the establishment of the definition of MetS, many studies have shown that it is highly correlated with future CVD and diabetes [2–4]. In other words, MetS is a reliable and accurate predictor.

At the same time, it is well-documented that hypertension strongly correlates with future CVD, insulin resistance and diabetes [5,6]. However, what is interesting and surprising is that the untoward effects of high blood pressure (BP) could even extend down to subjects with prehypertension [7–14]. For example, Vasan et al. had reported that prehypertension is associated with a hazard ratio of 1.6 (95% confidence interval, 1.1–2.2) for CVD in men than their normotensive counterparts in the Framingham study [9]. Three other studies also showed that prehypertension has been associated with increased thickness of the carotid intima and media, altered cardiac morphologic features and diastolic ventricular dysfunction, which may be the precursors of cardiovascular events [15–17].

However, two facts must be kept in mind when interpretating these data. First, some of these studies did not exclude subjects who were on medications for hypertension, hyperlipidemia, or diabetes [10–14]. In this case, it would be hard to avoid underestimating these parameters because the drug effects were crucial for these studies. Secondly, hypertension is well-known to be tightly correlated with age. Not all of these studies took age as a confounding factor and made adjustment accordingly. In spite of these two limitations, based on the aforementioned evidences, it would still be interesting to know whether the harmful

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effects of BP extend down to the subjects with normal BP, i.e. BP < 120/80 mmHg.

Since National Health Policy provides good quality of health care, the life expectancy of Taiwanese is much longer than before as many other developed countries in the world. Thus, this makes the geriatric medicine become an important area. Furthermore, aging is also proved to be related to the increased prevalence of MetS in male [18]. In this study, we enrolled 2388 normotensive older men in order to evaluate whether subjects with high-tertile SBP have higher risks for CVD and diabetes than those with low-tertile SBP. It should be noted that the original purpose of defining MetS was to predict future CVD and diabetes risks [19]. Therefore, we used MetS as having the risk for future CVD and diabetes.

Methods

Study participants

We enrolled subjects who underwent routine medical check-ups at MJ Health Screening center. It is the largest health screening center in Taiwan and has provided health screening services for over 1 million persons since its inception in 1988 [20]. Informed consents were collected from all anonymous participants and this study protocol was approved by the institutional review board of MJ Health Screening Center.

A total of 21318 males between 65 and 80 years old were enrolled from January 2009 to December 2011. The inclusion criteria of age equal to and over 65 years old was based on the WHO definition for gerontology [21,22]. We excluded subjects with a history of diabetes, hypertension, abnormal lipid profile, CVD and those taking medications for these diseases. Moreover, subjects with BP ≧ 120/80 mmHg were also excluded. At last, 2388 older men were qualified for further analysis.

To observe the relationships between BP and MetS components, we divided the study subjects into three groups according to their systolic BP (SBP). Since it is well-known that age is tightly related to one's BP [23], it would not be surprising that the group with highest SBP must be the oldest. Therefore, unique design was used to avoid this confounding factor. Two steps were taken to define the groups. First, subjects within the same age were divided into three subgroups according to their SBP tertiles. For example, subgroup-1 had the lowest SBP. Because the age of the study cohort was from 65 to 80 years and each age group had its own subgroups, there were 16 subgroup-1. Second, a larger and final Group-1 was formed by putting all the 16 subgroup-1 from each age stratum together. Thus, this Group-1 contained all the subjects with low-tertile SBP from each and every age stratum. Similarly, Group-2 with middle-tertile SBP and Group-3 with high-tertile SBP were also constructed similarly. In this way, one subject's SBP was only compared with other subjects who were in the same age group. By using this method, the bias from the age effect on the SBP could be adjusted. It should also be stressed that we used SBP rather than diastolic BP (DBP) as the criteria for grouping, which was based on the evidence that SBP was a better predictor for future CVD [24–27].

Anthropometric and laboratory data

The health examinations consisted of a medical history taking including the subject's current medication, a complete physical examination, BP, anthropometric measurements and fasting plasma blood samples. Trained senior nursing staffs took all the measurements. SBP and DBP were measured by nursing staff 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. The plasma was then measured for fasting plasma glucose (FPG) and lipid profiles. The 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.

Definition of the metabolic syndrome

To define MetS in this study, we used the Third Report of the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III) with some modification [19,28]. Waist circumference (WC) used to define central obesity is greater than 90 cm in men. This criterion was suggested by the International Obesity Task Force coordinated by the International Diabetes Institute and the Regional Office for the Western Pacific [29]. The other criteria included TG ≧ 150 mg/dL, FPG ≧ 100 mg/dL and HDL-C < 40 mg/dL for men. Since all the study subjects were normotensive, at least three out of four above mentioned components were needed to be present for the diagnosis of MetS.

Statistical analysis

SPSS version 19.0 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. The TG level was logarithmically transformed before analysis because it was not normally distributed. In addition, logistic regression analysis was performed to examine odds ratios (ORs) for having each abnormal MetS component or MetS itself among the three groups. Furthermore, Pearson's correlation was used to examine the correlations between each metabolic parameter and SBP. After that, multiple linear regression analysis was done to examine whether the significant related MetS components in the simple correlation were truly independent.

All statistical tests were two-sided and $p < 0.05$ was considered to be statistically significant.

Results

The baseline characteristics of the study subjects are shown in Table I. Due to our unique grouping method, the age in each group was matched. All the MetS components in Group-3, except for HDL-C, were significantly higher than Group-1. On the other hand, only WC and TG in Group-2 were significantly higher than Group-1.

To observe the relationships between SBP and age, WC, FPG, HDL-C, LDL-C and log TG, Person's correlation was performed. Only age, WC, FPG, HDL-C and log TG were significantly related to SBP. To further identify which of these five factors were independently related, multiple linear regression analysis was applied (Table II). Except for HDL-C, other previously significant factors remained significantly associated with SBP. Among them, WC had the greatest β value.

Figure 1 displays the prevalence of each abnormal MetS component. There were 64.8% of subjects with at least one abnormal MetS component (data not shown). The prevalence of the abnormal WC, HDL-C, FPG and TG were 19.5%, 20.2%, 45.2% and 19.6%, respectively. Totally, 9.9% subjects were defined as having MetS. The ORs for having each abnormal MetS component and MetS itself in Group-2 and Group-3 against Group-1 are showed in Table III. Group-3, except for HDL-C, has significant higher ORs for having abnormal WC, FPG, TG and MetS. On the other hand, Group-2 only had significant higher OR for having abnormal FPG.

Discussion

As the health caring system becomes more and more effective, aging is now a significant issue in Taiwan as many other developed countries. Therefore, health promotion and disease prevention are important policies in the older people for the Department of Health. In the meanwhile, coronary artery disease, cerebrovascular disease and diabetes are the 2nd, 3rd and 5th most common causes of death. Since the main purpose of the MetS is to prevent these diseases, the purpose of our study is important. In this study, we demonstrated that even the BP is within normal range, the higher it is, the more comorbidity it will cause.

Interestingly, compared with our previously published data in middle-aged men (40–65 years) [30], the present study showed nearly the same patterns of the relationships between BP and other MetS components. Not only the significant components related to BP, but also the orders of the ORs were the same. For example, the adiposity had the highest OR, and the risk for having abnormal HDL-C in subjects with high-tertile SBP did not reach the statistical significance. However, in middle-aged men, the high-tertile SBP group bore a 1.7-fold higher OR for having MetS than its low-tertile counterpart. Compared with the current study, the OR was only 1.55-fold. The possible explanation may be due to the effect of the age on the MetS components.

As mentioned in the introduction, we excluded subjects with treatments for any of the MetS components. Although this relatively stringent inclusion criterion could avoid the bias from the treatment, at the same time, this method might prohibit including subjects on the other extreme of the spectrum, i.e. subjects with overweight, low HDL-C, high TG or impaired glucose intolerance. Therefore, this would result in attenuation of the impact from the SBP on these four components. However, if the untoward effects of SBP could be proved in this relatively normal cohort, it could be premised that the similar phenomenon should only be worse in subjects with abnormal MetS. In fact, all other studies done in hypertension and prehypertension had shown this kind of results. Thus, this study could be regarded as a last piece of jigsaw puzzle to complete the whole picture of hypertension.

In this study, except for HDL-C, all other MetS components (WC, FPG, TG) were positively correlated with SBP. Among them, WC had the highest β value which indicated that it could explain most part of the changes of SBP. Similar findings could also be found in many other reports [12,31–34]. For example, in a cohort of 5050 Chinese men aged from 35 to 74 years, individuals with central obesity and overweight had a significantly higher prevalence of prehypertension than those with normal weight [33]. Another study done by Okosun et al. revealed that abdominal obesity is associated with increased risk of prehypertension in American men and women [34]. In their study, abdominal obesity was associated with increased risk of prehypertension in Whites, Blacks and Hispanics, independent of age, blood glucose, total cholesterol, exercise and current smoking. Again, it should be stressed that all the abovementioned studies only investigated the relationship

Table I. Clinical characteristics of the study subjects.

Characteristic	Total (n = 2388)	Group-1 (n = 796)	Group-2 (n = 796)	Group-3 (n = 796)	p value
Age (years)	68.5 ± 3.8	68.5 ± 3.8	68.5 ± 3.8	68.5 ± 3.8	0.998
WC (cm)	82.0 ± 8.6	80.6 ± 8.9	82.0 ± 8.4*	83.3 ± 8.4*,†	<0.001
BMI (Kg/m^2)	22.7 ± 2.9	22.2 ± 3.0	22.7 ± 2.8*	23.2 ± 2.7*,†	<0.001
SBP (mmHg)	110 ± 7.8	101 ± 5.7	111 ± 2.2*	118 ± 1.8*,†	<0.001
DBP (mmHg)	66 ± 6.8	63 ± 6.5	66 ± 6.3*	69 ± 6.1*,†	<0.001
FPG (mg/dL)	102 ± 22.6	101 ± 20.9	101 ± 18.4	105 ± 27.5*,†	0.003
Total cholesterol (mg/dL)	197 ± 35.1	196 ± 34.7	196 ± 35.1	198 ± 35.5	0.496
HDL-C (mg/dL)	51 ± 14.6	52 ± 14.8	52 ± 15.1	50 ± 13.6*	0.027
LDL-C (mg/dL)	123 ± 31.8	123 ± 30.8	121 ± 31.7	124 ± 32.7	0.301
Log TG	2.00 ± 0.20	1.98 ± 0.20	2.01 ± 0.21*	2.02 ± 0.20*	<0.001

Data are shown as mean ± standard deviation.
*p < 0.05 against Group-1; †p < 0.05 against Group-2.
BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; Log TG, log transformation of triglyceride; TG, triglyceride; SBP, systolic blood pressure; WC, waist circumference.

between "prehypertensive" versus "normotensive" subjects. Our finding further confirmed that the effect of obesity on SBP persisted even down to the normal range of BP.

In addition to the body weight, age is also well-documented to be positively correlated with SBP [23]. The exclusion of subjects with high BP in our study might obscure the true relationship between them. In this study, we chose the SBP as the criteria for grouping. Since age was positively correlated to SBP, it became a confounding factor to our study. Therefore, in this study, two different statistic methods were used to evaluate the relationships between SBP and other MetS components. When using the ANOVA to compare the differences of three groups, the confounding effects of age were adjusted by the grouping method. While in the multiple regression, the age was also adjusted by the statistic method itself. In brief, although age did affect the SBP in our study, and thus became a confounding factor, it has been skillfully adjusted in this study.

Table II. Multiple linear regression analysis between systolic blood pressure and age, metabolic syndrome components.

Variable	Parameter	β (95% CI)	*p* value
Systolic blood pressure	Age	0.049 (0.009 to 0.089)	0.016
	Waist circumference	0.134 (0.090 to 0.178)	<0.001
	Fasting plasma glucose	0.041 (0.001 to 0.081)	0.047
	High-density lipoprotein-cholesterol	0.036 (−0.010 to 0.082)	0.122
	Log triglyceride[a]	0.065 (0.019 to 0.111)	0.005

[a]Data were log-transformed.

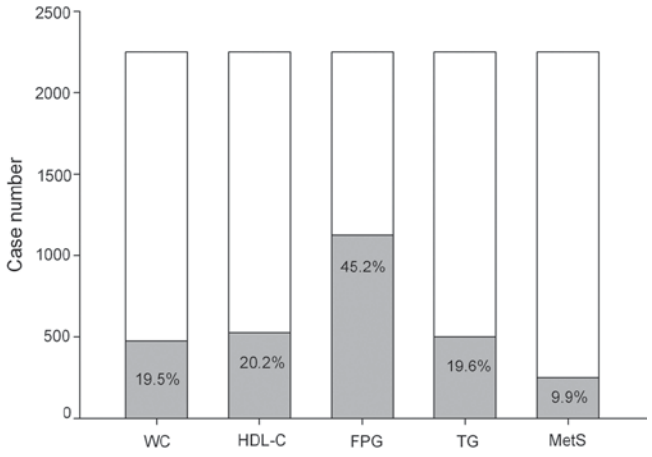

Figure 1. The percentage of each abnormal metabolic syndrome component and metabolic syndrome. WC, waist circumference; HDL-C, high-density lipoprotein-cholesterol; FPG, fasting plasma glucose; TG, triglycerides; MetS, metabolic syndrome.

It is reasonable to postulate that lower HDL-C and higher LDL-C are related to hypertension. However, this is not the case in many studies. From the literature search, different reports had non-consistent results concerning the HDL-C and LDL-C levels in prehypertensive subjects [12,13,32,33,35]. Our study showed that HDL-C and LDL-C were not significantly correlated with SBP in older men. This finding could be interpreted at least as a further confirmation for the loose correlation between them. On the other hand, subjects with medications for abnormal BP or hypercholesterolemia were excluded from this study, which might also contribute to the non-significant correlation. Contrary to the cholesterol, the positive correlation between TG and SBP was noted and this is concordant with most of the other studies [12,13,32,33,36]. Based on these findings, we can draw the conclusion that the predicting ability for future CVD and diabetes of both low HDL-C and high LDL-C are less evident than hypertriglyceridemia in older men. The importance of hypertriglyceridemia should be stressed in older men with normotension.

Compiling evidences suggested that hypertension and prehypertension were positively associated with higher FPG [10,12,13,32,33,35–37]. Similar results were also found in our study even in normotensive subjects. This is not surprising because insulin resistance (IR) is considered to be the core of MetS [29]. High BP is proved repeatedly in different studies to be related to IR. Our data suggest that even in subjects with normotension, the correlation between SBP and FPG could still be noted. In other words, subjects with high-tertile SBP were still under higher risk for MetS in the future.

It should be stressed that in this study, we were not trying to state that normotensive subjects with high-tertile SBP should be treated. This issue is beyond the scope of our present study. However, we still consider that our data could evoke some interesting questions about the role of BP even when

Table III. Prevalence and odds ratios (95% CI) for components of metabolic syndrome in tertiles of systolic blood pressure.

		Group-1	Group-2	Group-3
WC ≥ 90 cm	Prevalence (%)	17	18	24
	ORs (95% CI)	1 (Ref.)	1.110 (0.857–1.439)	1.552 (1.212–1.988)*
FPG ≥ 100 mg/dL	Prevalence (%)	40	46	50
	ORs (95% CI)	1 (Ref.)	1.286 (1.054–1.570)*	1.519 (1.245–1.853)†
HDL-C < 40 mg/dL	Prevalence (%)	19	21	21
	ORs (95% CI)	1 (Ref.)	1.154 (0.901–1.477)	1.180 (0.922–1.510)
TG ≥ 150 mg/dL	Prevalence (%)	16	20	22
	ORs (95% CI)	1 (Ref.)	1.267 (0.981–1.636)	1.473 (1.146–1.892)*
MetS	Prevalence (%)	8	9	12
	ORs (95% CI)	1 (Ref.)	1.134 (0.801–1.605)	1.553 (1.118–2.158)*

*$p < 0.05$; †$p < 0.001$, OR was adjusted for age, smoking and exercise.
CI, confidence interval; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein-cholesterol; MetS, metabolic syndrome; ORs, odds ratios; TG, triglycerides; WC, waist circumference.

it is still within its normal range. For instance, it is generally thought that the correlation between BP and its co-morbidity is J-shaped [38,39]. However, we proved otherwise. It seems that the lower BP, the less chance to have MetS in this group of older men. Based on this observation, the next question would be "Would there be beneficial effects if we treat normotensive subjects with high-tertile BP to low-tertile BP?" These interesting questions are remained to be answered in the future studies with better designs.

Several potential limitations should be noted concerning this study. First, this is a cross-sectional study and the study cases were from health check-ups. Compared to a longitudinal and randomized selected design, our results were less convincing. However, these two limitations could all be justified by the present large study cohort. We still believed that our results shed light on the role of SBP in this particular group of subjects. Further studies are certainly needed to verify our findings. Secondly, this study was only done in Taiwanese older men. Therefore, ethnic differences should also be kept in mind while exploration our data to other populations.

In conclusion, the current study showed that normotensive older men with high-tertile SBP would have higher chance of having increased WC, FPG, TG and, therefore, MetS itself. Thus, they are more prone to have future CVD and diabetes compared to those with low-tertile SBP. Education and lifestyle modification might be important in this particular group of subjects.

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Declaration of Interest: The authors declare no conflict of interest.

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