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Metabolic syndrome and its components in relation to brachial-ankle pulse wave velocity in middle-aged Taiwanese males

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Abstract: To evaluate the association of The study is to evaluate the association of metabolic syndrome (MS) and its components on brachial-ankle pulse wave velocity (baPWV), an indirect marker of subclinical atherosclerosis, in middle-aged Taiwanese males. A total of 442 men aged 40 to 65 years were included in this cross-sectional survey. Arterial stiffness was measured using a non-invasive method by baPWV. MS is defined by the presence of $\geq$ 3 components using the modified National Cholesterol Education Program criteria. The mean baPWV was 1478.6 and 1520.3 cm/sec in normal-weight and overweight adults, respectively. Age, systolic blood pressure (BP), diastolic BP, and fasting blood glucose (FBG) correlated with baPWV levels in normal-weight and overweight males. In multiple logistic regression analysis, after adjusting for potential confounders, MS and its components (such as high BP and high FBG) were significantly associated with abnormal baPWV ($\geq$1400 cm/sec) ($p < 0.001$). MS and its components are significantly associated with abnormal baPWV in Taiwanese middle-aged males and in addition, high BP was the component of MS most significantly associated with abnormal baPWV.

Keywords: high blood pressure, metabolic syndrome, brachial-ankle pulse wave velocity

1 Introduction

Over the past decades, chronic diseases such as cardiovascular disease (CVD), diabetes mellitus type 2 and stroke have accounted for a significant fraction of the mortality in

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developed and developing countries, including Taiwan [1, 2]. Several studies have shown that cigarette smoking, high blood pressure (BP), obesity and hyperlipidemia, are risk factors associated with the occurrence of CVD [3–6]. Furthermore, a combination of the multiple CVD and metabolic risk factors may have more influence than a single risk factor [7, 8].

Metabolic syndrome (MS) was first defined by a committee of experts from the World Health Organization (WHO) in 1998 [9]. Furthermore, the WHO and the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III established the diagnostic criteria for this syndrome [10]. Currently, there is plenty of data in the literature showing an increased risk of CVD in people with MS [7, 8, 11–14]. At the same time MS is frequently worsened by the incidence and progression of carotid atherosclerosis in the general population. The screening of individuals with MS is conceivably useful from the public health standpoint since they could benefit from interventions aimed at reducing CVD risk.

Pulse wave velocity (PWV), a non-invasive arterial stiffness index, is an indicator of early-stage atherosclerosis and the development of CVD. It is generally used to help identify high risk patients with arterial stiffness. Recently, many studies have shown that increased PWV is positively associated with the occurrence of atherosclerosis in diabetic [15–18], hypertensive [6, 19, 20] or end-stage renal disease patients in late life [21, 22]. Overall, high PWV is associated with increased CVD risk factors and events.

The purpose of our study is to evaluate the association of MS and its components on brachial-ankle pulse wave velocity (baPWV) and to find out which of these components is the most significant factor associated with sub-clinical atherosclerosis among Taiwanese males.

2 Statistical methods and Experimental Procedures

2.1 Study Design and Patients

We conducted a cross-sectional health check-up survey in Taiwan males in 2003. Totally of 442 middle age males (40 to 65 years old) completed a questionnaire about their cardiovascular disease history and lifestyle characteristics (such as cigarette smoking and alcohol consumption). The participants were measured anthropometric parameters (such as body height, body weight, waist circumference and blood pressure), and also collected blood specimen after 12 hours fasting in this survey. The Ethical Committee of the Scientific Institute approved this study and informed consent was obtained from the subjects.

2.2 Anthropometrics and Blood Pressure Measurement

Research technicians measured body weight to an accuracy of 0.1 kg using a segmental body composition analyzer (Tanita Corp., Tokyo, Japan) [23] with subjects barefoot and

wearing light indoor clothing. Body height was recorded to the nearest 0.5 cm using a ruler attached to the scale. We calculated their body mass index (BMI) as body weight (kg) divided by the square of their height (m). Moreover, overweight was defined as BMI $\geq$ 25 kg/m^2 and normal-weight was defined as BMI<25 kg/m^2. Waist circumference was measured at the midpoint between the inferior margin of the last rib and the iliac crest in the mid-axillary plane to the nearest 0.1 cm [24].

After resting for 10 min in sitting position, we measured the blood pressure (BP) on the right arm using an appropriate cuff size by HEM-740C automatic digital BP monitor (Omron Corp., Tokyo, Japan). We measured the BP again after 5 min of rest and the average was used in the analysis.

2.3 Lipids and Lipoprotein Measurement

To reduce person to person variation, we collected a 12 hour fasting blood sample only from subjects who had maintained their usual diet in the past three days. Serum glucose and triglyceride (TG) concentrations were analyzed immediately; other assays were performed, such as the biochemical assays for lipoprotein within one week of the blood samples being stored at -4 °C. We measured serum concentrations of TG using an enzymatic procedure, and glucose using the glucose oxidase method on the Hitachi 7150 autoanalyzer (Hitachi, Tokyo, Japan). High density lipoprotein cholesterol (HDL-C) was measured by an enzymatic method with magnesium precipitation using the Olympus AU600 autoanalyzer (Olympus, Tokyo, Japan).

2.4 Arterial Stiffness Measurement

We measured bilateral brachial-ankle PWV (baPWV) as a class index of non-invasive arterial stiffness by Colin VP-1000 instrument (Colin Corp., Komaki, Japan). This device records heart sounds, electrocardiogram, BP, and PWV simultaneously [15, 25]. A microphone for detecting heart sounds was placed on the left edge of sternum, electrodes of electrocardiogram were placed on both wrists, and four cuffs were wrapped on both brachia and ankles with the subjects in the supine position. The cuffs were connected to an oscillometric pressure sensor that measures blood pressure and a plethymographic sensor that determines the volume pulse waveform. This device can record pulse waveforms and store them from the start point of each pulse wave in the right arm to both legs in its memory, and record the time difference between transmission time to arm and transmission time to ankle as "transmission time". Then, the device uses the body height to calculate the transmission distance from the right arm to each ankle, and automatically computes the right baPWV and left baPWV values by transmission time and transmission distance (cm/sec). We measured the PWV on both sides (right baPWV and left baPWV) and used the mean right/left baPWV value in our study's analysis. The validation of this automatic method and its reproducibility were reported with an intra-observer repeatability coefficient of 0.94 and an inter-observer reproducibility coefficient of 0.89 [25].

2.5 Definition of Metabolic Syndrome

Metabolic syndrome (MS) was defined using the modified National Cholesterol Education Program (NCEP) criteria [10, 26]. High BP is defined as subjects on antihypertensive medication or systolic BP (SBP) $\geq$ 130 mmHg or diastolic BP (DBP) $\geq$ 85 mmHg. Hypertriglyceridemia is defined as subjects on triglyceride (TG) medication or TG $\geq$ 150 mg/dl. Low HDL-C, $\leq$ 40 mg/dl in men. High fasting blood glucose (FBG) level is defined as subjects on hypoglycemic medication or FBG $\geq$110 mg/dl. Abdominal obesity is defined as waist circumference $\geq$ 90 cm in men. In this study, MS is diagnosed if any three or more of the above-mentioned abnormal values is present. Since there is no clear cut-off point for abnormal baPWV, we considered a value greater than 1400 cm/sec as abnormal [27].

2.6 Statistic Analysis

We used the mean and standard deviation to describe the distribution of anthropometric parameters, BP, biochemical levels and baPWV with body weight specification. At the same time ,we used numbers and percentage to demonstrate the distribution of lifestyle status and history of CVD. The Student t test or Pearson chi-square test was used to determine the differences of anthropometric parameters, BP, biochemical levels, baPWV levels, lifestyle status, and history of CVD among males of different weights. Spearman correlation analysis was used to establish the relationship between baPWV and CVD risk factors of MS. Logistic regression analysis using abnormal baPWV ($\geq$1400 cm/sec) as a dependent variable was conducted to evaluate the association of MS and its components as independent with and without adjustment for age, cigarette smoking, alcohol drinking, history of CVD, and BMI. Furthermore, we examined the association of abnormal baPWV between MS and its components after adjusting for potential confounders. We also investigated which component of MS is most significantly associated with abnormal baPWV among adults, using multiple logistic regressions with standardized coefficients with and without adjustment for potential confounders. All statistical analysis were conducted using the statistical package SAS 8.2 (SAS institute Inc, Cary, NC, USA) and $p<0.05$ as statistical significance.

3 Results

In this study, we included 442 males with a mean age of 51.7 $\pm$ 5.8 years old (40 to 65 years old). The anthropometric parameters data, BP, biochemical level, baPWV, lifestyle and history of cardiovascular diseases in normal and overweight subjects are shown in Table 1. In general, overweight males had larger waist circumference, higher BP, TG and FBG levels and lower HDL-C than normal weight individuals (all $p < 0.05$). They also had a higher prevalence of MS and history of cardiovascular disease, but lower prevalence of alcohol drinking.

Table 1 General characteristic of study subjects.

Variables	Normal-weight(n=214) (BMI<25 kg/m^2) Mean±SD	Overweight(n=228) (BMI ≥ 25 kg/m^2) Mean±SD	t/x^2 test
Age (year)	51.9±5.6	51.5±5.9	0.59
Cigarette smoking[1]			3.56
No	129(60.3)	157(68.9)	
Yes	85(39.7)	71(31.1)	
Alcohol drinking[1]			4.17 *
No	176(82.2)	203(89.0)	
Yes	38(17.8)	25(11.0)	
History of CVD [1]			7.26 **
No	152(71.0)	134(58.8)	
Yes	62(29.0)	94(41.2)	
BMI (kg/m^2)	22.9±1.7	27.6±2.3	24.82 ***
Waist circumference (cm)	82.4±5.6	91.6±6.1	16.50 ***
SBP (mmHg)	128.5±17.0	135.7±16.4	4.52 ***
DBP (mmHg)	83.0±11.4	88.5±11.7	5.03 ***
HDL-C (mg/dl)	49.0±10.4	45.7±9.6	3.50 ***
TG (mg/dl)	132.0±66.8	160.1±73.5	4.73 ***
FBG (mg/dl)	93.9±27.1	105.8±33.6	4.10 ***
baPWV (cm/sec)	1478.6±234.5	1520.3±262.9	1.76
Metabolic syndrome [1]			52.03 ***
No	190(88.8)	133(58.3)	
Yes	24(11.2)	95(41.7)	
Abnormal baPWV [1]			0.31
No	91(42.5)	91(39.9)	
Yes	123(57.5)	137(60.1)	

Abbreviations: BMI, body mass index; SD, standard deviation; CVD, cardiovascular disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; FBG, fasting blood glucose; baPWV, brachial-ankle pulse wave velocity. [1] number (percent).

Table 2 shows the Spearman correlation coefficient of baPWV levels on age, anthropometrics parameters, BP and biochemical risk factors among males in different weight ranges. The baPWW levels have significant positive correlation with age, SBP, DBP, and FBG in both weight types; but correlate with TG only in normal weight individuals (all $p < 0.05$).

Table 3 presents the association of MS and its components with abnormal baPWV in males. In both with and without MS, the mean baPWV of study subjects are 1565.6±262.7 cm/sec and 1476.0±241.4 cm/sec, respectively. Furthermore, after adjusting for age, cigarette smoking, alcohol drinking, history of CVD and BMI, MS is also significantly associated with abnormal baPWV (OR=1.86, 95%CI=1.11-3.16). In addition, we examined subjects with MS components and abnormal baPWV with and without adjusting for potential confounders. We found that by they having 1, 2, or ≥ 3 of the components of MS put them at increased risk and that there was a significant association with abnormal baPWV (adjusted OR=2.60, 95%CI=1.28-5.43; adjusted OR=4.62, 95%CI=2.17-10.17; adjusted OR=4.24, 95%CI=1.82-120.25, respectively) than

Table 2 Spearman correlation analyses between pulse wave velocity and the components of metabolic syndrome in males with different weight status.

Variables	Normal-weight (n=214) (BMI<25 kg/m^2)		Overweight (n=228) (BMI $\geq$ 25 kg/m^2)	
	Coefficients	p-value	Coefficients	p-value
Age (year)	0.38	< 0.0001	0.28	< 0.0001
Waist circumference (cm)	0.08	0.23	0.06	0.36
SBP (mmHg)	0.57	< 0.0001	0.58	< 0.0001
DBP (mmHg)	0.56	< 0.0001	0.52	< 0.0001
HDL-C (mg/dl)	0.09	0.20	0.02	0.80
TG (mg/dl)	0.14	0.04	0.03	0.61
FBG (mg/dl)	0.27	< 0.0001	0.19	<0.01

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; FBG, fasting blood glucose. *p<0.05, **p<0.01, ***p<0.001.

when compared with those without any MS component. Moreover, we also found a statistical significance between the number of MS components and an abnormal baPWV (adjusted p for trend 0.0004). As components of the MS analysis, high BP and FBG are significantly associated with abnormal baPWV with or without adjustment for potential confounders.

The comparison of the significance of the MS components on abnormal baPWV among males is shown on Table 4. Based on Table 3, we selected the BP and FBG together using standardized coefficients to see which components were more significantly associated with abnormal baPWV in multiple logistic regression analysis. Both were, but the BP component was the most significantly associated with an abnormal baPWV (standardized coefficient 0.455 vs. 0.178). Even adjusting for potential confounders, this association was still significant (p<0.0001) but the one for FBG was not significant($p = 0.10$).

4 Discussion

In this study, we found that middle-aged men with MS are at increased risk of having an abnormal baPWV when compared to those without it. The mean baPWV of study subjects was 1565.6±262.7 cm/sec and 1476.0±241.4 cm/sec in both with and without MS, respectively. Also, the more components of MS present, the higher risk of arterial stiffness. Furthermore, high BP was the component of MS most significantly associated with abnormal baPWV after adjusting for potential confounders.

Although our study found that BP and FBG are associated with an abnormal baPWV it had some potential limitations. First, the study design is a cross-sectional survey, which does not allow us to draw conclusions in terms of causality between MS and arterial stiffness. Second, only males were included in this study and it may not apply to women. Third, we used the modified National Cholesterol Education Program (NCEP) criteria to define metabolic syndrome, which may be less restrictive in certain parameters. However,

Table 3 Logistic regression analyses of metabolic syndrome and its components on abnormal pulse wave velocity (1400 cm/sec) among male adults

Independent variables	Model I		Model II	
	OR	95%CI	OR	95%CI
MS [1]				
Yes/ No	2.11	1.35-3.36	1.86	1.11-3.16
Features of MS[2]				
0	1.00		1.00	
1	2.44	1.36-4.47	2.60	1.28-5.43
2	3.70	2.05-6.80	4.62	2.17-10.17
>=3	4.90	2.67-9.21	4.24	1.82-10.25
Components of MS				
High blood pressure [3]				
Yes/ No	5.45	3.61-8.31	5.62	3.61-8.88
Fasting blood glucose [4]				
$\geq$ 110 mg/dl/<110 mg/dl	2.33	1.37-4.11	1.84	1.05-3.34
Waist circumference				
$\geq$ 90 cm/<90 cm	1.43	0.96-2.16	1.10	0.64-1.90
Triglyceride [5]				
$\geq$150 mg/dl/<150 mg/dl	1.33	0.90-1.97	1.29	0.85-1.98
HDL-C				
<40 mg/dl/$\geq$40 mg/dl	0.86	0.55-1.34	0.71	0.44-1.15

Abbreviations: OR, odds ratio; CI, confidence interval; MS, metabolic syndrome; HDL-C, high-density lipoprotein cholesterol. Model I, simple variable analyses (including only one independent variable); Model II, adjusting for age, cigarette smoking, alcohol drinking, history of cardiovascular disease, and body mass index. [1] Without MS, including zero, one, and two components of MS.- [2] and test for trend p<0.001 in both model I and model II. [3] High blood pressure, subjects with antihypertensive medication or systolic blood pressure $\geq$ 130 mmHg or diastolic blood pressure $\geq$ 85 mmHg. [4] Abnormal fasting blood glucose, including subjects with anti-glucose medication. [5] Hypertriglyceridemia, including subjects with lipid-lowering medication.

Table 4 Multiple logistic regression analyses of the components of metabolic syndrome on abnormal pulse wave velocity (1400 cm/sec) with male adults.

	Model I			Model II		
	Standardized coefficients	Wald X^2	p value	Standardized coefficients	Wald X^2	p value
Components of MS						
High blood pressure [1]						
Yes/No	0.455	63.42	< 0.0001	0.459	55.18	< 0.0001
Fasting blood glucose [2]						
$\geq$ 110 mg/dl/<110 mg/dl	0.178	9.09	< 0.01	0.110	2.77	0.10

[1] High blood pressure, subjects with antihypertensive medication or systolic blood pressure $\geq$130 mmHg or diastolic blood pressure $\geq$ 85 mmHg. [2] Abnormal fasting blood glucose, including subjects with anti-glucose medication. Model I, multiple variable analyses (including variables of high blood pressure and fasting blood glucose status); Model II, adjusting for age, cigarette smoking, alcohol drinking, history of cardiovascular disease, and body mass index.

it was more appropriate for community screening. Our paper's purpose was to find any markers that could be more useful in the pre-disease stage. Fourth, measurement errors may have occurred even with careful training. We trained our staff on how to conduct the study and instrument calibration before exams to reduce measurement error. However,

these errors may be minimal and may have only attenuated our final result. Finally, baPWV is an indirect marker of arterial stiffness, since it includes the stiffness of both elastic-type and muscular-type arteries. As these two types of arteries have different wall composition, they have different determinants of stiffness. Therefore, we could not determine the relative influence of arterial wall remodeling on the relationship between MS and arterial stiffness. To determine the precise effect of MS on arterial stiffness, the use of ultrasound technology, which can estimate both morphological and functional parameters (stiffness), may be preferable.

PWV was determined by measuring brachial-to-ankle transit time in the aorta, which offers a simple, reliable and non-invasive evaluation of regional aortic stiffness. The path length determined from superficial linear measurements could be underestimated and possibly corrected based on the anatomic dimensions of the body due to longer and more tortuous arteries with age [5, 6, 28]. However, Lerbun and colleagues consider the error in the distance is relatively small and do not affect the results significantly. Besides, the differences in body composition of male and female may account for this PWV [4, 29]. In our analysis, all the subjects were male and age adjustment was done to avoid any potential underestimation of their association.

Many studies have shown that MS is associated with an increase in CVD morbidity and mortality [7, 11] and MS is also associated with the progression of carotid atherosclerosis [13, 14, 30]. Similar to our results, the baPWV in the MS group is greater than the non-MS group (1565.6 cm/sec vs. 1476.0 cm/sec). The contribution of each sub-clinical component to atherosclerosis may be small. Since based on the MS definition, subjects without MS also may have zero, one, and two components of MS. These results suggest that clinicians need to pay attention to this problem. In addition, having multiple components may exert greater influence on atherosclerosis even at the sub-clinical stage. Furthermore, the more the components of MS that are present, the higher the risk of developing atherosclerosis in our study, the odds ratio rose from 2.60 (95%CI=1.28-5.43) to 4.24 (95%CI=1.82-10.25) for those with 1 component to those who had 3 or more MS components (adjusted p for trend 0.0004). Recent studies have also shown that clustered features of MS are strongly associated with an increased risk of elevated baPWV in men [8, 12]. In the Bonora study, investigators also considered that identification of a single risk factor and correction should be replaced by targeting individuals with the cluster and tailoring treatment possibly on the underlying mechanisms [7]. In our study, we found that the components of MS (such as high blood pressure and FBG, but not the lipid profiles) were the significant factors associated with an abnormal baPWV, and this was slightly different from other studies [13, 14].

The accumulation of glycosylation end products on matrix proteins in the vessel walls may modify directly the elastic properties of arteries, with a consequent increase in arterial stiffness [5, 18, 31, 32]. Furthermore, the increase of glucose and insulin levels may be associated with greater vascular glycosylation end products [3, 5]. In our results, the association of blood glucose level on baPWV was consistent, which suggested that the blood glucose level may be as important as the BP on arterial stiffness among male

Taiwanese adults. In addition, Cruickshank and colleagues show that PWV is a powerful independent predictor of mortality in both patients with diabetes mellitus and people with an abnormal glucose-tolerance-test and take the SBP as a prognostic factor that may be useful in conjunction to evaluate the vascular status [16].

Many epidemiological studies have revealed that BP or pulse blood pressure (PP) was positively associated with PWV and was the most important CVD risk factor [3–5, 18, 20, 33–35]. Arterial stiffness, premature return of reflected waves in late systolic pulse, is associated with an increased central pulse pressure and the load on the ventricle which is also associated with a reduction in ejection fraction and an increase in myocardial oxygen demand [36–39]. Some studies have suggested that BP has the same denominator as PWV, resulting in an increase in arterial stiffness and significant CVD risk [4, 5, 19]. In our study, after adjusting for potential confounders, BP is positively associated with elevated baPWV levels. Recent studies have shown that anthropometric parameters were not significantly associated with elevated PWV levels [4–6, 8, 20, 28, 33, 34]. Our results showed no association between waist circumference and arterial stiffness after adjusting for potential confounders.

In conclusion, we found that MS and its components such as high BP and FBG are significantly associated with abnormal baPWV in Taiwanese males. In conjunction the MS components had a greater impact than those without MS on sub-clinical atherosclerosis. Furthermore, this study provides evidence that high BP is the most important risk factor for the early detection of atherosclerosis. Perhaps, this suggests that MS is not really a significant entity; rather it is just a conglomerate of features that tend to group together. Therefore, it would be better to pay more attention to BP monitoring in the evaluation of MS and controlling of hypertension. Finally, more intervention programs are needed to evaluate the effectiveness of preventing MS or reducing the risk of cardiovascular disease (or atherosclerosis).

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