Metabolic syndrome is associated with change in subclinical arterial stiffness

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Abstract

Objectives: The aim of this study was to evaluate the effect of MetS on subclinical arterial stiffness in a longitudinal study.

Methods: Brachial-ankle pulse wave velocity (baPWV), a measurement interpreted as subclinical arterial stiffness, was measured in 1518 community-dwelling persons at baseline and re-examined within a mean follow-up period of 3 years. Multivariate linear regression with generalized estimating equations (GEE) were used to examine the longitudinal relationship between MetS and its individual components and baPWV, while multivariate logistic regression with GEE was used to examine the longitudinal relationship between MetS and its individual components and the high risk group with subclinical arterial stiffness.

Results: Subjects with MetS showed significantly greater baPWV at the end point than those without MetS, after adjusting for age, gender, education, hypertension medication and mean arterial pressure (MAP). MetS was associated with the top quartile of baPWV (the high-risk group of subclinical arterial stiffness, adjusted odds ratio [95% confidence interval] 1.52 [1.21-1.90]), and a significant linear trend of risk for the number of components of MetS was found (p for trend <0.05). In further considering the individual MetS component, elevated blood pressure and fasting glucose significantly predicted a high risk of subclinical arterial stiffness (adjusted OR [95% CI] 3.72 [2.81-4.93] and 1.35 [1.08-1.68], respectively).

Conclusions: MetS affects the subject's progression to subclinical arterial stiffness. Subclinical arterial stiffness increased as the number of MetS components increased. Management of MetS is important for preventing the progression to advanced arterial stiffness.

Keywords: metabolic syndrome; pulse wave velocity; prediction

Introduction

Metabolic syndrome (MetS), defined as a cluster of features such as visceral obesity, impaired glucose tolerance, dyslipidemia, hypergtriglyceridemia, and elevated blood pressure [1, 2], is highly prevalent all over the world [3-5]. MetS has been known as a critical risk factor in the incidence of type 2 diabetes and in cardiovascular outcome [1, 6, 7]. People with MetS have higher all-cause or cardiovascular mortality than those without MetS [8, 9]. Subclinical arterial stiffness, a pathological condition with vascular damage, is a cardiovascular outcome of MetS. In clinical practice, pulse wave velocity (PWV) is widely used to reflect subclinical arterial stiffness. A noninvasive brachial-ankle pulse wave velocity (baPWV) measurement, which is performed more easily than carotid-femoral PWV measurement, has been used as a marker for screening vascular damage and cardiovascular risk in the general population [10], in diabetes patients [11], in hypertension patients [12], in patients with end-stage renal disease [13], and in women with systemic lupus erythematosus [14].

The association of MetS with subclinical arterial stiffness has been investigated in many studies [15-19]; however, most of these studies were cross-sectional [15-17, 19]. Those studies which explored the longitudinal effect of MetS on arterial stiffness were conducted in disease–specific or hospital-based population [20-22], or in persons presenting for a work-related health check-up [23]. A limited number of studies have been conducted in the general population. Identifying the effect of MetS on arterial stiffness using a longitudinal study can provide information for the management of MetS and thereby prevent progression to advanced arterial vascular disease. Therefore, the objective of the current study was to evaluate the longitudinal effect of MetS on baPWV by considering mean arterial pressure (MAP) and the use of hypertension medicine to reduce the influence of blood pressure on baPWV.

Methods

Study sample

This was a population-based follow-up study. The design and selection criteria of the Taichung Community Health Study (TCHS) have been described previously.[24] Briefly, 4,280 individuals were randomly selected from Taichung City, Taiwan to be representative of its residents in terms of sex and age (aged 40 and over). Data on 2,359 individuals (about 66.83% of the original sample) were collected from 2004-2005, and 2,311 survivors were contacted 3 years later for re-examination. A total of 1,648 subjects were followed (overall follow-up rate, 71.3%) before the end of July, 2009. Of those, 28 were excluded from this analysis because they did not have a baPWV measurement at baseline or follow-up, 100 were excluded because they had suspected peripheral arterial stiffness (ankle-brachial index <0.9 at baseline), and 2 were excluded because of missing smoking status at baseline. In the end, 1,518 individuals (mean age, 56 years; 49% women) remained eligible for data analysis. All subjects signed an informed consent form before data collection.

Measurements

Anthropometric measurements and laboratory examination

All study subjects underwent a physical examination measuring height, waist circumference (WC), and blood pressure by trained staff at baseline, as well as at the endpoint. MAP was calculated as (2 ×diastolic blood pressure + systolic blood pressure) ÷3. Blood was drawn with minimal trauma from an antecubital vein in the morning, after a 12-hour overnight fasting, and was sent for analysis within four hours of collection. Biochemical markers such as HDL cholesterol, triglyceride, fasting glucose, fasting insulin, urine albumin and creatinine were analyzed by a biochemical autoanalyzer (Beckman Coluter, Lx-20, USA) at the Clinical Laboratory Department of China Medical University Hospital.

Sociodemographic factors, lifestyle factors and medical history

Data on sociodemographic factors (including age, gender and education), lifestyle factors, and medical history were collected by self-administered questionnaires. Lifestyle factors, such as smoking and alcohol drinking history, were categorized as never and former/current. We collected self-reported personal medical histories, including diabetes and hypertension medication at the baseline and follow-up examination.

MetS and its components

MetS was defined clinically, based on the presence of three or more of the following American Heart Association and the National Heart Lung Blood Institute(AHA/NHLBI) MetS criteria [2]: (1) central obesity (WC ≥90 cm in men, and ≥80 cm in women), (2) high triglycerides level (≥1.7mmol/L or on drug treatment for elevated triglycerides), [25] low HDL-C level (<1.03 mmol/L in men and <1.30 mmol/L in women or on drug treatment for reduced HDL-C), (4) high blood pressure (systolic BP ≥130 mmHg or diastolic BP ≥85 mmHg or under anti-hypertensive drug treatment in a patient with a history of hypertension), and (5) high fasting plasma glucose concentration (≥5.5 mmol/L or on drug treatment for elevated glucose). Diabetes was defined as fasting plasma glucose concentration ≥7.0 mmol/L or on drug treatment for diabetes. Hypertension was defined as systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg or on drug treatment for hypertension.

Longitudinal changes in subclinical arterial stiffness

BaPWV, presenting for subclinical arterial stiffness, was measured non-invasively with subjects in the supine position and with a VP-1000 automated PWV/ABI analyzer (PWV/ABI; Colin Co. Ltd., Komaki, Japan) attached to the four limbs [26]. For every subject, the maximum of the left and right baPWV was chosen at baseline and at follow-up. The change in baPWV was calculated as re-examined

baPWV subtracting baseline baPWV.

Statistical analysis

Continuous variables were reported as mean ± standard deviation (SD) and categorical variables were reported as percentage (95% confidence intervals, abbreviated as CI). To explore the effect of MetS and its components on baPWV, four multivariate models were used. First, the variables that predicted the baPWV change were evaluated with multivariate linear regression after multivariate adjustment. Second, the longitudinal effect of MetS and the number of components in the baPWV were examined using multivariate linear regression with the GEE method. Third, we further evaluated how the longitudinal effect of individual MetS components on baPWV was affected by the other components being considered sequentially, using hierarchical regression analysis with the GEE approach. The order of entering the variables was elevated blood pressure, fasting glucose, WC, triglyceride, and low HDL cholesterol after adjustment. Last, the top quartile of baseline baPWV was used as the cutoff point to classify the high risk group with subclinical arterial stiffness. Multivariate logistic regression with the GEE approach was used to analyze the longitudinal effect of MetS and its components on subclinical arterial stiffness. We treated the number of MetS components as continuous variables to examine the linear trend on the risk of subclinical arterial stiffness. All reported *p* values were those of the two-sided tests; statistical significance was set at $p < 0.05$. All analyses were performed using SAS version 9.1 (SAS Institute Inc, Cary, NC).

Results

Compared with individuals without MetS, a higher proportion of individuals with MetS were older, male, with ≤ 9 years of educational attainment, former or current smokers, former or current drinkers, and users of hypertension, hyperlipidemia, and diabetes medication (Table 1).

The baseline baPWV and changes in baPWV during the follow-up period, according to the various groups of sociodemographic factors, health factors, and medication after adjusting for baPWV at baseline, are illustrated in Table 2. Larger increases in changes of baPWV were observed in those with an older age, lower educational level, and use of medication for hypertension, hyperlipidemia, and diabetes at baseline (all $p<0.05$). The changes were not significantly different in terms of marital status and health factors at baseline, such as smoking and drinking.

Subjects with MetS had a higher mean value of baPWV at baseline. Compared to subjects without MetS, subjects with MetS had a significantly greater 3-year mean change of baPWV (-9.5 vs. 31.1, after adjusting for baPWV at baseline) (Table 3). The greater the number of MetS components at baseline, the larger the adjusted mean changes of baPWV (p for trend <0.001).

Analysis of the longitudinal effect of MetS on baPWV using GEE models showed that subjects with MetS had a higher mean baPWV of 36.8 ($p<0.001$) after adjusting for age, gender, education, time-dependent hypertension medication, and time-dependent MAP. Considering the longitudinal effect of the number of MetS components on baPWV, the differences in baPWV in subjects with 1, 2 and more than or equal to 3 MetS components versus those without a MetS component were 37.8, 46.2 and 75.9, respectively (all $p<0.001$) (data not shown).

In exploring the independent effects of MetS components, hierarchical regression analysis with the GEE approach demonstrated that elevated blood pressure (adjusted

regression coefficients [β]=28.4, $p<0.001$) and fasting glucose (β=51.7, $p<0.001$) had an independent effect on longitudinal baPWV (Table 4).

The cutoff point of the top quartile of baseline baPWV was 1813 cm/s. The adjusted odds of the high-risk group with subclinical arterial stiffness for MetS were 1.52 (95% confidence interval [CI], 1.21-1.90). The adjusted odds ratios (ORs) of the high-risk group with arterial stiffness were 3.31 (95% CI, 2.06-5.33), 4.21 (95% CI, 2.57-6.91), and 5.24 (95% CI, 3.20-8.57) in subjects with 1, 2, and ≥3 MetS components after multivariate adjustment. A significant linear relationship between the adjusted OR and the number of components of MetS was found (p for trend <0.05). The adjusted ORs of the high-risk group with arterial stiffness were 3.72 (95% CI, 2.81-4.93) and 1.35 (95% CI, 1.08-1.68) in individuals with elevated blood pressure and fasting glucose (both p <0.05) (Fig 1).

Discussion

In this 3-year community-based prospective study, we found that MetS and the MetS components independently predicted the future progression or incidence of subclinical arterial stiffness. Regarding the influence of individual components of MetS on arterial stiffness, we found that blood pressure and fasting glucose were independent determinants of longitudinal arterial stiffness progression in this general population. Moreover, they were independent risk factors for predicting the 3-year incidence of the higher risk of developing subclinical arterial stiffness.

The existence of a strong association between the presence of MetS and arterial stiffness has been shown in many cross-sectional studies [15-17]. However, the longitudinal effect of MetS on arterial stiffness in the general population has not been clarified [23, 27, 28]. In this longitudinal population-based study, we provided community-based evidence that MetS is an independent risk factor for progression of subclinical arterial stiffness in a random sample of Taiwaneses adults aged 40 years and over. Our findings were consistent with those of several previous studies that showed a causal relationship between MetS and arterial stiffness. In a 3-year prospective study of 2,080 male employees in a company, Tomiyama et al. showed that subjects with persistent MetS had a higher annual rate of increase in baPWV than those with regression of MetS during the follow-up period [23]. Similar deleterious effects of MetS on aortic stiffness were found in a 6-year follow-up study of a health check-up for 476 French adults who were working and retired persons and their families [28].

In the present study, only elevated blood pressure and fasting glucose were independent predictors of progressive subclinical arterial stiffness. Tomiyama et al. [23], in their study of 2080 male employees aged 29 to 76 years with an average of 3 years of follow-up, found elevated blood pressure and fasting glucose at baseline were independent predictors for changes in baPWV, which was consistent with our findings.

Li et al [27] followed 835 young adults aged 4 to 17 years with 26.5 years in average, and found that the independent predictors of baPWV in young adults were systolic blood pressure, HDL cholesterol, and triglycerides in adulthood. However, we did not find that elevated triglyceride and low HDL cholesterol were associated with longitudinal baPWV. There are two possible reasons why Li et al.'s findings [27] were not consistent with ours. One is that they did not measure baPWV at baseline and could not correct or adjust it, which may have resulted in overestimating the effects of triglyceride and HDL cholesterol. The other is that our study lacked power to detect the effect of triglyceride and HDL cholesterol, due to the shorter follow-up period than that in Li et al's study [27].

The possible mechanism that can explain the effect of elevated blood pressure on progressive arterial stiffness is its direct effect on arterial walls. Elevated blood pressure may accelerate arterial stiffening because it forces endothelial cells and arterial smooth muscle cells to be exposed to the increase arterial wall dispensability chronically, which reflects arterial stiffening [29]. Elevated blood glucose leads to the formation and deposition of advanced glycation end-products, which promote the crosslinking of collagen that stiffens the structural components of the arterial wall [30].

This study has several strengths. First, this was a prospective study; therefore, the temporal relationship between metabolic risk factors and arterial stiffness could be clearly ascertained. Second, this was a community-based cohort which could be representative of the general population. And lastly, our study evaluated arterial stiffness using non-invasive and simple baPWV measurement, and statistical corrections were made to prevent the influence of blood pressure. However, there are two limitations to our study. One is that our findings could not be generalized to young adults because we recruited participants aged 40 and over. The other is that the findings of our study may not be generalized to adults living in areas of less urbanization, because our sample was

randomly selected from a population in a metropolitan area.

Conclusions

We found that MetS and its components of fasting glucose and blood pressure are independent predictors of the longitudinal increase in subclinical arterial stiffness. Since these predictors are associated with significant cardiovascular morbidity and mortality, our findings suggest that management of MetS to prevent progression to advanced arterial vascular disease is important.

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