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Baseline forced expiratory volume in the first second as an independent predictor of development of the metabolic syndrome

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Abstract

A growing body of evidence strongly supports associations between reduced lung function and insulin resistance, type 2 diabetes mellitus, and cardiovascular disease. The present study was undertaken to explore the possibility that reduced lung function is an independent predictor of development of the metabolic syndrome (MetS) and to investigate potential links between reduced lung function and the MetS. A prospective cohort study of reduced lung function as a predictor of subsequent MetS was conducted using 2-year follow-up data for 450 middle-aged adults lacking the MetS at baseline. Data were obtained from the Taipei MJ Health Screening Centers in Taiwan. The *MetS* was defined according to the modified Adult Treatment Panel III criteria. Over 2 years of follow-up, 26 of the 450 subjects (5.78%) without the MetS at baseline subsequently developed the syndrome. In multiple logistic regression analysis with adjustments for age, sex, body mass index, cigarette smoking, alcohol consumption, and physical activities, reduced forced expiratory volume in the first second (FEV_1) at baseline remained a predictor of subsequent MetS (relative risk of 4.644, $P = .036$ for the third [<2.31 L] vs first [>2.88 L] tertile). In Pearson and partial correlation analyses, white blood cell counts and C-reactive protein concentrations were both found to be significantly and negatively correlated with FEV_1. Lower FEV_1 is concluded to serve as an independent predictor of the MetS. Low-grade systemic inflammation is the possible link between reduced lung function and the MetS.

1. Introduction

The metabolic syndrome (MetS), comprising insulin resistance, central obesity, dyslipidemia, and hypertension, is associated with the development of type 2 diabetes mellitus and increased cardiovascular mortality [1-4]. The syndrome was initially known as the *insulin resistance syndrome* because insulin resistance may serve as a primary link between the various components of the MetS [5]. Moreover, the MetS is now accepted to be a proinflammatory state and strongly associated with excess adiposity [6]. The excess adipose tissue commonly observed in subjects with the MetS promotes the overproduction of inflammatory cytokines that, in turn, influence the actions of insulin and exacerbate insulin resistance [7].

Findings of several recent studies indicate that impaired lung function, as measured by forced vital capacity (FVC) or forced expiratory volume in the first sec (FEV_1), is a powerful predictor of nonfatal ischemic heart disease and cardiovascular mortality [8-10]. A substantial body of evidence supports the hypothesis that the relationship between reduced lung function and vascular disease is mediated by low-grade systemic inflammation [8,11,12] even in the absence of overt pulmonary disease [13]. In addition, reduced lung function has been found to be associated with excess adiposity [14,15], insulin resistance [16,17], and type 2 diabetes mellitus [17,18].

Current findings are consistent with the possibility that systemic inflammation, insulin resistance, and excess

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adiposity mediate the relationship between reduced lung function and the MetS. In a recent study involving a Chinese cohort, restrictive lung impairment was found to be associated with an increased risk for development of the MetS [19]. However, this study was limited by its cross-sectional design. Furthermore, the increased risk for acquiring the MetS was observed mainly for subjects with restrictive lung impairment as compared with subjects without lung impairment. The present longitudinal study was therefore conducted to examine directly the associations of FVC and FEV_1 with the MetS in a middle-aged Chinese cohort. An additional objective was to explore potential links between reduced lung function and development of the MetS.

2. Subjects and methods

2.1. Subjects

Data were obtained from the Taipei MJ Health Screening Centers in Taiwan from 2003 to 2005. The MJ Health Screening Centers provided a multidisciplinary team approach for their members, with annual or biannual health assessment by registered health practitioners. A total of 700 individuals attending the Centers for health examinations completed the 2-year follow-up. To avoid factors with the potential to affect the results of the lung function tests, subjects with any history of, or treatments for, major systemic diseases such as chronic lung diseases, asthma, or autoimmune disease (n = 20) were excluded. Subjects who had developed the MetS at the start of the study (n = 163), those who did not complete the questionnaire (n = 25), and those who did not take the lung function tests (n = 42) were also excluded. A totally of 450 subjects (239 men and 211 women) were enrolled for analysis.

Baseline examinations including anthropometric and blood pressure measurements, physical examinations, and assessments of nutritional status were performed in 2003. Each examinee completed a self-administered questionnaire at the time of examination and screening. Information concerning social condition, education, income, lifestyle factors including cigarette smoking and alcohol consumption, and personal and family histories of major chronic diseases was collected. Blood samples were taken for biochemical analyses after at least 12 hours of fasting. Two years later (2005), subjects were asked to return for follow-up studies. The same examinations and questionnaire were administered. The protocol for this research was approved by the Review Committee at the MJ Health Screening Center, and all data were treated anonymously.

2.2. Data collection

Body weight and height were measured with an autoanthropometer (Nakamura KN-5000A, Tokyo, Japan). Body weight was measured to the nearest 0.1 kg with the subject barefoot and wearing light indoor clothing. Body height was recorded to the nearest 0.1 cm. Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters. Waist circumference (WC) was taken at the midway point between the inferior margin of the last rib and the crest of the ilium in a horizontal plane and measured to the nearest 0.1 cm. Hip circumference was measured around the pelvis at the point of maximal protrusion of the buttocks and was determined to the nearest 0.1 cm. Blood pressure was measured twice, on the right arm, with the subject in a sitting position, after 5 minutes of rest, using a computerized auto–mercury-sphygmomanometer (Citizen CH-5000; Citizen, Tokyo, Japan). Two measurements were taken at 10-minute intervals. The mean of these 2 readings was used in analysis.

A venous blood sample was collected after 12 hours of fasting for determinations of fasting plasma glucose, triglycerides, high-density lipoprotein cholesterol (HDL-C), and C-reactive protein (CRP) using a Hitachi 7150 autoanalyzer (Tokyo, Japan). White blood cell (WBC) counts were determined using an Abbott Cell Dyn 3000 hematology analyzer (Abbott Laboratories, Abbott Park, IL). All specimens were analyzed by the central laboratory at the MJ Health Screening Center. This laboratory uses strict internal and external quality control techniques. Standards for calibration were supplied by the manufacturer.

Lung function tests were performed for every subject by an experienced technician using an automated flow-sensing spirometer (Microspiro HI-500, Tokyo, Japan) according to the recommendations of the American Thoracic Society [20]. All lung function tests were performed with the subject in the sitting position. If at all possible, at least 3, but no more than 8, forced expiratory maneuvers were performed in an effort to meet the American Thoracic Society standards. Values selected for the study were FVC and FEV_1. The best FVC and FEV_1 values obtained from the 3 or more tests with acceptable curves were used for analysis. All subjects were classified into tertiles with respect to FEV_1.

Using the questionnaire, subjects were classified as never smokers, former smokers (those who reported any prior use of cigarettes), and current smokers (those who reported the use of cigarettes at the time of the study). *Current* and *never alcohol drinkers* were defined as those who reported drinking alcohol at least once and less than once per week, respectively. Physical activity was divided into 3 levels. *None/mild physical activity* was defined as less than 1 hour of exercise per week. *Moderate physical activity* was defined as 1 to 3 hours of exercise per week. *Vigorous physical activity* was defined as more than 3 hours of exercise per week.

2.3. Definition of the MetS

The *MetS* was defined clinically, based on the presence of 3 or more of the following modified Adult Treatment Panel III criteria [21]: central obesity (with WC cut points of $\geq$90 cm for Taiwanese men and $\geq$80 cm for Taiwanese women),

an elevated triglyceride value (≥1.7 mmol/L or drug treatment of elevated triglycerides), a reduced HDL-C value (<1.03 mmol/L for men and <1.29 mmol/L for women or drug treatment of reduced HDL-C), elevated blood pressure (≥130 mm Hg for systolic blood pressure, ≥85 mm Hg for diastolic blood pressure, or antihypertensive drug treatment in a patient with a history of hypertension), and an elevated fasting plasma glucose concentration (≥5.6 mmol/L or drug treatment of diabetes).

2.4. Statistical analysis

Data are presented as means ± standard deviations unless indicated otherwise. Baseline characteristics of subjects who developed the MetS during the course of the study and of controls were compared by the Student *t* test for continuous variables and by Pearson χ^2 test for categorical variables. The Wald χ^2 test was used to evaluate the statistical significance and relative risks (RRs) of the prevalence rates of the MetS. Multiple logistic regression analysis was used to estimate the RR of the MetS by age, sex, BMI, tertiles of FEV_1, cigarette smoking, alcohol consumption, and physical activity. Correlations between FEV_1 and WBC counts/CRP concentrations were calculated using the Pearson correlation coefficient and the partial correlation coefficient where appropriate. Calculations were performed using the SPSS statistical package version 15.0 (SPSS, Chicago, IL). A *P* value (2-sided) of < .05 was considered to be significant.

3. Results

A total of 26 subjects (5.78%) developed the MetS over the 2-year follow-up period. Their baseline characteristics are presented in Table 1. Notably, the mean age, WC, BMI, triglyceride concentration, HDL-C, fasting plasma glucose, systolic blood pressure, and FEV_1 were higher in those who subsequently developed the MetS as compared with controls. However, no significant differences were observed as a function of sex (*P* = .608), mean diastolic blood pressure (*P* = .129), mean FVC (*P* = .182), alcohol consumption (*P* = .733), cigarette smoking (*P* = .528), or physical activity (*P* = .323).

Table 2 shows the results of a multivariate logistic regression analysis with the MetS as the outcome variable. After adjusting for age, sex, BMI, alcohol consumption, cigarette smoking, and physical activity, subjects in the third tertile (<2.31 L) for FEV_1 were found to be 4.644-fold (*P* = .036) more likely to develop the MetS as compared with those in the first tertile (>2.88 L). By contrast, FVC did not independently predict development of the MetS in multivariate analysis (data not shown). Moreover, age, BMI, and physical activity were observed to be independent predictors of the MetS. With increasing age and BMI, the risk for development of the MetS increased significantly. The RR for acquiring the MetS was significantly higher in subjects with none/mild physical activity as compared with those with vigorous physical activity (3.407, *P* = .046).

Table 1
Baseline demographic and metabolic characteristics of study subjects

Baseline characteristics	Results at 2-y follow up		
	Did not develop MetS	Developed MetS	*P* value
n	424	26	
Age (y)	43 ± 11	49 ± 13	.004
Men (n, %)	225 (53.07)	14 (53.85)	.938
WC (cm)	79.0 ± 8.2	83.9 ± 9.5	.004
BMI (kg/m^2)	22.4 ± 2.6	24.8 ± 2.8	<.001
Triglycerides (mmol/L)	1.10 ± 0.65	1.69 ± 0.79	<.001
HDL-C (mmol/L)	1.56 ± 0.39	1.36 ± 0.33	.011
Fasting plasma glucose (mmol/L)	5.42 ± 0.51	5.90 ± 1.41	<.001
Systolic blood pressure (mm Hg)	117 ± 16	123 ± 14	.039
Diastolic blood pressure (mm Hg)	70 ± 10	73 ± 9	.129
WBC ($\times 10^6/\mu L$)	6.16 ± 1.56	6.80 ± 1.64	.837
CRP (mg/L)	0.25 ± 0.37	0.40 ± 0.43	.073
FVC (L)	2.92 ± 0.74	2.72 ± 0.87	.182
FEV_1 (L)	2.63 ± 0.65	2.26 ± 1.00	.005
Alcohol consumption (%)[a]			.733
Never	86.1	88.5	
Current	13.9	11.5	
Cigarette smoking (%)[a]			.582
Never	72.4	65.4	
Former	5.4	3.8	
Current	22.2	30.8	
Physical activity (%)[a]			.323
Vigorous	19.3	11.6	
Moderate	41.1	34.6	
None/mild	39.6	53.8	

Data are shown as means ± standard deviations.

[a] Cigarette smoking, alcohol consumption, and physical activity were categorized as described in methods and procedures.

To explore the role of systemic inflammation in linking FEV_1 with development of MetS, we assessed the relationship between WBC counts, CRP concentrations, and FEV_1. The correlation coefficients are summarized in Table 3. White blood cell counts and CRP concentrations correlated significantly and negatively with FEV_1. After correction for age, sex, and cigarette smoking, both correlations remained significant.

4. Discussion

The present study is the first to demonstrate that FEV_1 can be used to predict development of the MetS in a middle-aged Chinese cohort independent of age, sex, BMI, alcohol consumption, cigarette smoking, and physical activity. Furthermore, findings of this study reveal a significant association of FEV_1 with WBC counts and CRP concentrations after correction for age, sex, and cigarette smoking. These associations highlight the likelihood of important linkage between FEV_1 and the MetS.

Although the pathophysiologic consequences of the MetS remain controversial, insulin resistance is thought to serve at the "core" of this syndrome [22]. Findings of the present study regarding decreased lung function and the occurrence

Table 2
Relative risks (95% confidence interval) for developing the MetS derived from a multiple logistic regression analysis using age, sex, BMI, FEV_1, alcohol drinking, smoking, and physical activity as independent variables

Variable	RR (95% CI)	*P* value
Age	1.047 (1.008-1.088)	.017
Sex		
Women	1.00 (reference)	
Men	1.241 (0.411-3.743)	.701
BMI	1.429 (1.213-1.684)	<.001
Tertile of FEV_1 (L)		
>2.88	1.00 (reference)	
2.31-2.88	2.118 (0.545-8.227)	.278
<2.31	4.644 (1.101-19.585)	.036
Alcohol consumption[a]		
Never	1.00 (reference)	
Current	0.856 (0.203-3.617)	.833
Cigarette smoking[a]		
Never	1.00 (reference)	
Former	1.247 (0.131-11.905)	.848
Current	1.968 (0.693-5.591)	.204
Physical activity[a]		
Vigorous	1.00 (reference)	
Moderate	2.065 (0.526-8.105)	.298
None/mild	3.407 (1.025-11.324)	.046

CI indicates confidence interval.
[a] Cigarette smoking, alcohol consumption, and physical activity were categorized as described in methods and procedures.

of insulin resistance as defined by increased fasting plasma glucose values are generally consistent with previous studies. For example, in a cross-sectional study of 3911 British women, Lawlor et al [17] observed an inverse association between one measure of insulin resistance and either FEV_1 or FVC after adjustment for important adult confounding factors. In the Normative Aging Study, Lazarus et al [16], who studied 1050 initially nondiabetic healthy men, found that lower FEV_1, lower FVC, and lower maximal midexpiratory flow rates at baseline predicted insulin resistance over 20 years of follow-up independently of age, BMI, waist-hip ratio, and cigarette smoking. In addition, findings of 3 prospective studies [18,23,24] revealed that subjects with lower ventilatory function have an increased risk of developing insulin resistance and type 2 diabetes mellitus. In contrast to the present study, these prospective studies involved white subjects only, used mathematical measurements of insulin resistance, and did not examine the association of lung function with the occurrence of the MetS. Findings of the present study reveal a lower FEV_1 at baseline as an independent predictor of the occurrence of the MetS.

Smoking can induce insulin resistance and represents a known risk factor for development of the MetS [25,26]. In a recent cross-sectional analysis of 1146 Taiwanese men, Chen et al [27] observed that current smokers had a higher prevalence of the MetS as compared with those who never smoked or who quit smoking. Furthermore, this study revealed a statistically significant and dose-dependent association of current smoking amount with development of the MetS. In the present study, however, cigarette smoking was not found to be an independent predictor of occurrence of the MetS. This discrepancy may be due to the incomplete smoking history, including pack-year of smoking, or to the short duration of follow-up for subjects in the present study. The finding of the present study that none/mild physical activity is associated with increased risk of developing the MetS is fully consistent with previous studies [28-30]. In addition, the finding of the present study that alcohol consumption is not significantly associated with occurrence of the MetS is in agreement with the 3-year longitudinal observation of the French DESIR (Data from an Epidemiological Study on the Insulin Resistance syndrome) cohort [31].

Increases in WBC counts and CRP concentrations are considered general markers of inflammation; in the present study, WBC and CRP values were found to correlate significantly and negatively with FEV_1 (Table 3). We propose the possibility that systemic low-grade inflammation could serve to link reduced lung function with development of the MetS. Previous findings of studies with healthy subjects are also consistent with linkage between low-grade systemic inflammation and reduced lung function [12,13,32]. In addition, Rutter et al [33] found that systemic inflammation correlates positively with the MetS. Furthermore, in a longitudinal analysis of Pima Indians, Vozarova et al [34] observed that low-grade systemic inflammation is positively associated with adiposity, insulin resistance, and development of the MetS. Similar findings have been reported by others [35,36]. The MetS is now accepted as a proinflammatory state [6]. The consequential overproduction of inflammatory cytokines may play an important role linked to the activation and adhesion of inflammatory cells to the pulmonary capillary endothelium, leading to changes in endothelial function and damage to air exchange. Certainly, the possible mechanisms that link impaired lung function to the MetS require further study to be investigated.

Certain limitations to this study should be considered. Firstly, subjects of the study were principally Chinese. Hence, findings may not prove applicable to other populations or ethnic groups. Secondly, data on oxygen saturation and birth weight and details regarding prepubertal development, each of which may influence lung function, β-cell function, and insulin resistance, were not available. Finally,

Table 3
Correlations between FEV_1 and WBC counts/CRP concentrations at baseline in all subjects

	WBC ($\times 10^9$/L), r	CRP (mg/L), r
FEV_1 (L)		
Pearson correlation coefficient	−0.108*	−0.145†
Partial correlation coefficient[a]	−0.127†	−0.167‡

r indicates correlation coefficient.
[a] Corrected for age, sex, and cigarette smoking.
* <.05.
† <.01.
‡ <.001.

WBC counts and CRP values, rather than specific inflammatory markers, were used as measures of low-grade systemic inflammation. Investigations designed to address these issues are planned.

Based on the findings of the present study, a reduction in the FEV_1 is proposed as a novel and useful predictor of the MetS. Low-grade systemic inflammation is hypothesized to mediate the link between a lower FEV_1 and development of the MetS. It is suggested that impairment of lung function be regarded as an early manifestation of the MetS and that determination of the FEV_1 should serve to detect subjects at risk for developing the MetS. Such early detection should lead to effective interventions aimed at primary prevention of the syndrome.

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