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Impact of respiratory function on the progression from metabolically healthy non-overweight to metabolically abnormal phenotype

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Abstract *Background and aims:* Recent studies identified that metabolically abnormal non-overweight phenotype is a risk factor for cardiovascular diseases. However, only little is known about risk factors for the progression from metabolically healthy non-overweight (MHNO) to metabolically abnormal phenotype. In this study, we investigated the impact of respiratory function on the progression from MHNO to metabolically abnormal phenotype.

Methods and results: In this retrospective cohort study, 8949 (3872 men and 5077 women) individuals with MHNO, who participated in a health-checkup program from 2004 to 2015, were enrolled. Four metabolic factors (high-normal blood pressure or hypertension, impaired fasting glucose or diabetes, hypertriglyceridemia, and low HDL cholesterol concentration) were used to define metabolically healthy (less than two factors) or metabolically abnormal (two or more factors) phenotypes. Respiratory function was measured by spirometry.

Over a median 4.0 years of follow-up, 927 participants progressed to metabolically abnormal phenotype. The percentage of FVC for predicted values (HR 0.98, 95% CI 0.93–1.03, $p = 0.418$) was not associated with the progression to metabolically abnormal phenotype after adjusting for covariates, including age, sex, alcohol consumption, exercise, smoking status, and body mass index, whereas the percentage of FEV_1 for predicted values (%FEV_1) (HR 0.87, 95% CI 0.84–0.91, $p < 0.001$) and the FEV_1/FVC ratio (HR 0.86, 95% CI 0.78–0.95, $p = 0.004$) were associated with the progression to metabolically abnormal phenotype.

Conclusion: Decrease in respiratory function in terms of %FEV_1 and the FEV_1/FVC ratio is associated with the progression to metabolically abnormal phenotype in individuals with MHNO.

Introduction

Metabolic syndrome is known as a risk factor for several life-threatening diseases such as diabetes [1,2], chronic kidney diseases [3], and cardiovascular diseases [2]. Obesity and metabolic syndrome are closely associated [4]. Metabolically healthy obesity (MHO) phenotype, which is known as relatively healthy obesity [5], is also a risk factor

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for diabetes, chronic kidney diseases, and cardiovascular diseases [6,7]. Furthermore, the risks of diabetes [8], chronic kidney diseases [3], and cardiovascular diseases [9] are higher in metabolically abnormal non-overweight (MANO) phenotype than those in MHO phenotype. It was reported that in Asia, many patients with diabetes or metabolic syndrome are individuals who are non-overweight [10]. Therefore, we need to pay more attention to MANO; this is useful for clinical setting to clarify the risk factor for the progression from metabolically healthy to metabolically abnormal (MA) phenotype in individuals with MHNO.

Chronic obstructive pulmonary disease (COPD) has a close association with insulin resistance, through systemic inflammation [11]. However, no previous studies revealed the association between respiratory function and the progression from MHNO to MA phenotype. In this historical cohort study, therefore, we investigated the association between respiratory function and the progression from MHNO to MA phenotype.

Methods

Study participants and study design

To clarify the impact of respiratory function on the progression from MHNO to MA phenotype, we performed a historical cohort study using data collected from a medical health-checkup program at Murakami Memorial Hospital, Gifu, Japan; NAGALA (NAfld in Gifu Area, Longitudinal Analysis) study. The purpose and the detailed characteristics of NAGALA study are described elsewhere [4]. This study was approved by the Ethics Committee of Murakami Memorial Hospital and conducted in accordance with the Declaration of Helsinki. The data of individuals were stored in a database after informed consent and personal identity information were obtained.

In the current study, we extracted the data of participants who received this medical checkup from 2004 to 2015. Exclusion criteria were missing data on covariates, including body mass index (BMI), lifestyle factors, and respiratory function, any medication usage, obese individuals, MA phenotype at baseline examination, and no follow-up examination.

Data collection

Medical history and lifestyle factors were evaluated using a standardized self-administered questionnaire. Data on alcohol consumption, the amount and type of alcohol consumed per week during the past 1 month, were obtained, and then, the mean ethanol intake per week was estimated [12]. The participants were divided into the following four groups: non or minimal alcohol consumption, <40 g/week; light alcohol consumption, 40–140 g/week; moderate alcohol consumption, 140–280 g/week; and heavy alcohol consumption, >280 g/week [12]. With regard to smoking status, the participants were categorized into three groups: never-, ex-, and current smokers. We also calculated pack-year by multiplying the number of cigarette packs smoked per day by the number of years of smoking [13]. With regard to exercise information, the type, frequency, and duration of participation in sports or recreational activities were evaluated using the questionnaire, and we defined regular exercisers as participants who performed any kind of sports at least once a week regularly [14]. We calculated BMI as weight in kilograms divided by height in meters squared. After an overnight fast, venous blood was collected, and the concentrations of several parameters including high-density lipoprotein (HDL) cholesterol, triglycerides, and fasting plasma glucose were determined.

Definitions of metabolic phenotypes

We defined overweight as BMI ≥23.0 kg/m^2, which has been proposed as a cutoff in Asia [15]. This definition was often used in Japan [10,16]. Four metabolic factors (high-normal blood pressure or hypertension, elevated triglycerides, low HDL cholesterol concentration, and impaired fasting plasma glucose or diabetes) were evaluated to determine whether the participant was metabolically healthy or abnormal [3]. Impaired fasting glucose and diabetes were considered when individuals' fasting plasma glucose was ≥5.6 mmol/L and ≥7.0 mmol/L, respectively, or when they were under medical treatment [17]. Hypertension was considered when individuals' systolic blood pressure was ≥130 mmHg and/or diastolic blood pressure was ≥85 mmHg and/or when they were under medical treatment [18]. Elevated triglyceride level was considered as >1.7 mmol/L or when the individuals were being treated for hyperlipidemia, and low HDL cholesterol was indicated by <1.03 mmol/L in men and <1.29 mmol/L in women [3]. An individual was considered as metabolically healthy or metabolically abnormal if none or one of the metabolic factors or if two or more metabolic factors were present [3], respectively.

Respiratory function data

A spirometer was used to measure the respiratory function. Forced vital capacity (FVC, L) and forced expiratory volume in 1 s (FEV_1, L) were determined by trained technicians according to the American Thoracic Society acceptability and reproducibility criteria [19]. Predicted values were based on the height, age, and gender; the predicated FVC was as follows: 0.045* height (cm)-0.023*age-2.258 for men and 0.032*height (cm)-0.018*age-1.178 for women, and the predicted FEV_1 was as follows: 0.036*height (cm)-0.028*age-1.178 for men and 0.022*height (cm)-0.022*age-0.005 for women [20]. The percentage of FVC for predicted values (%FVC, %) was calculated as FVC/the predicated FVC, and the percentage of FEV_1 for predicted values (%FEV_1, %) was calculated as FEV_1/the predicated FEV_1. In addition, the FEV_1/FVC ratio was calculated [21].

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