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The "cardiometabolic index" as a new marker determined by adiposity and blood lipids for discrimination of diabetes mellitus

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ABSTRACT

Background: Patients with type 2 diabetes are prone to have obesity and dyslipidemia. The purpose of this study was to evaluate the usefulness of cardiometabolic index (CMI), a new index calculated as the product of waist-to-height ratio and triglycerides-to-HDL cholesterol ratio, for discrimination of diabetes.
Methods: Subjects were 10,196 Japanese women and men who had received annual health checkups at their workplaces. Receiver-operating characteristic (ROC) analysis and logistic regression analysis were performed to determine relationships of CMI with hyperglycemia and diabetes.
Results: In women and men, hemoglobin A1c was significantly higher in the highest quartile of CMI than in the other lower quartiles. By using ROC analysis, the cutoff values of CMI for hyperglycemia and diabetes were determined to be 0.799 and 0.800, respectively, in women and to be 1.625 and 1.748, respectively, in men. When these cutoff values were used in logistic regression analysis, there were strong associations of CMI with hyperglycemia and diabetes in women and men (odds ratio with 95% confidence interval of subjects with vs. subjects without high CMI: 6.98 [4.68–10.42] for hyperglycemia and 14.61 [5.95–35.88] for diabetes in women; 4.42 [3.66–5.35] for hyperglycemia and 5.38 [3.89–7.44] for diabetes in men).
Conclusion: The results suggest that CMI is a useful new index, reflecting both adiposity and blood lipids, for discrimination of diabetes.

1. Introduction

Patients with diabetes are prone to have dyslipidemia such as high triglyceridemia, low HDL cholesterolemia, and a preponderance of atherogenic small, dense LDL particles [1,2]. A high prevalence of dyslipidemia in patients with diabetes contributes to the pathogenesis of atherosclerotic macrovascular disease, which strongly influences their prognosis. Some lipid-related indices to monitor patients for prediction of cardiovascular disease have been proposed. The ratio of LDL cholesterol to HDL cholesterol and the ratio of total cholesterol to HDL cholesterol are classical atherogenic indices [3,4]. The ratio of triglycerides to HDL cholesterol (TG/HDL-C ratio) has been proposed to be a good discriminator for cardiovascular risk [5,6]. TG/HDL-C ratio has been shown to reflect atherogenic small dense LDL particles [7] and to be associated with insulin resistance [8] and metabolic syndrome [9].

More recently, lipid accumulation product (LAP), a continuous marker of lipid over-accumulation, has been proposed to be a good predictor for cardiovascular disease [10] and diabetes [11]. LAP is calculated by using the waist circumference (WC) and triglyceride level (TG) as LAP = TG (mmol/l) × (WC (cm) − 58) for women and LAP = TG (mmol/l) × (WC (cm) − 65) for men [10]. Thus, different corrections of waist circumference are used to calculate LAP in women and men, and comparison of LAP between them is difficult. It is also inconvenient that LAP becomes minus (under-zero) level when waist circumferences are <58 cm in women and 65 cm in men. Waist circumference is a simple marker for abdominal obesity, and waist circumference corrected by height (waist-to-height ratio, WHtR) has been proposed to be a more reasonable index than waist circumference for abdominal obesity [12]. WHtR has been shown to be a better discriminator of coronary heart disease and cardiovascular risk factors than waist circumference and body mass index (BMI) [13–15]. We here propose a new index, named cardiometabolic index (CMI), calculated as the product of TG/HDL-C ratio and WHtR,

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which are a good predictor of coronary artery disease [5,6] and a central component of metabolic syndrome [16], respectively. All of the components consisting of CMI are included in the criteria of metabolic syndrome [16]. Relations of CMI to hyperglycemia and diabetes were investigated in this study.

2. Methods

2.1. Subjects

The subjects were Japanese women (n = 3282) and men (n = 6914) aged 35–40 years who had received periodic health checkup examinations at workplaces and had been registered in a population-based database in Yamagata Prefecture in Japan. This study was approved by the Ethics Committee of Yamagata University School of Medicine (No. 112 from April 2005 to March 2006, approved on March 13, 2006). A population-based database including the results of annual health checkup examinations, in which the participants were not identified, was used, and informed consent from each participant was not obtained in this study. This procedure was approved by the institutional ethics committee. Those who had been receiving drug therapy for dyslipidemia (1.1%) were excluded from subjects of this study. Histories of illness, medication, alcohol consumption, cigarette smoking, and regular exercise (almost every day with exercise for ≥30 min/day) were surveyed by questionnaires. The subjects were divided into three groups by average cigarette consumption (nonsmokers; light smokers, ≤20 cigarettes/day; heavy smokers, >20 cigarettes/day). Average alcohol consumption of each subject per week was reported on questionnaires. The subjects were divided into three groups (nondrinkers, occasional drinkers and regular drinkers) by frequency of drinking.

2.2. Measurements

Waist circumference was measured at the navel level according to the recommendation of the definition of the Japanese Committee for the Diagnostic Criteria of Metabolic Syndrome [17]. BMI was calculated as weight in kilograms divided by the square of height in meters. Fasted blood was sampled from each subject, and serum triglycerides and HDL cholesterol were measured by enzymatic methods using commercial kits, Pureauto S TG-N and Cholestest N-HDL (Sekisui Medical Co., Ltd.), respectively. CMI was calculated as the product of WHtR and TG/HDL-C ratio.

Blood hemoglobin A1c was used for evaluation of hyperglycemia. Hemoglobin A1c was determined by the latex cohesion method using a commercial kit (Determiner HbA1c, Kyowa Medex). CVs for each measurement were ≤3% for triglycerides and ≤5% for HDL cholesterol and hemoglobin A1c. Hemoglobin A1c values were calibrated by using a formula proposed by the Japan Diabetes Society (JDS) as hemoglobin A1c (National Glycohemoglobin Standardization Program) (%) = 1.02 × hemoglobin A1c (JDS) (%) + 0.25 (%) [18]. Subjects with diabetes were defined as those showing high hemoglobin A1c levels (≥6.5%), according to the criteria for diagnosis of diabetes by the American Diabetes Association [19]. Hyperglycemia including diabetes and prediabetes was defined as hemoglobin A1c ≥ 5.7% [19]. Subjects receiving drug therapy for diabetes were also included in the hyperglycemia and diabetes groups.

2.3. Statistical analysis

Statistical analyses were performed using computer software programs (SPSS ver 16.0J). Mean levels of each variable were compared between women and men using unpaired Student's *t* test. Since triglycerides, TG/HDL-C ratio and CMI did not show normal distributions, they were compared between groups non-parametrically by using the Mann–Whitney *U* test. Difference in proportions was compared using the chi-square test for independence. The values of CMI in subjects were arranged in ascending order, and then the subjects were divided into four quartile groups of approximately equal sizes. Mean levels of hemoglobin A1c were compared among the four quartile groups of CMI by using analysis of variance (ANOVA) followed by Scheffé's F-test as a post-hoc test in univariate analysis and by using analysis of covariance (ANCOVA) followed by Student's *t*-test after Bonferroni correction in multivariate analysis. In correlation and multiple regression analyses, Pearson correlation coefficients and standardized regression coefficients were estimated. How well CMI for prognostic risk prediction could separate those who did and did not have diabetes or hyperglycemia was evaluated using the receiver-operating characteristic (ROC) curve [20]. Sensitivity and specificity are the basic measures of accuracy of a diagnostic test: The sensitivity is the probability of a positive test result, while the specificity is the probability of a negative test result. ROC is a plot of sensitivity versus 1-specificity that offers a summary of sensitivity and specificity across a range of cut points for a continuous predictor. The optimal cutoff point was selected by maximizing Youden's index, which is the difference between the true positive rate (sensitivity) and the false positive rate (1-specificity) in the ROC curve. Discrimination was measured by the area under the ROC curve (AUC). AUC and 95% confidence interval were estimated empirically. ROC was analyzed by using an open-source package for R [21]. Pairwise comparison of AUCs among the groups (for waist circumference, BMI, triglycerides, LAP and CMI) was performed by using the DeLong method [22] with Bonferroni correction for multiplicity of testing. In logistic regression analysis, odds ratios for hyperglycemia or diabetes were estimated in subjects with vs. subjects without high CMI, defined by using the cutoff values determined in this study. The discriminant accuracy of the resultant logistic regression model was also assessed using the percentage of correct prediction. Age and histories of smoking, alcohol drinking and regular exercise were used as other explanatory variables and covariates in multivariate analyses. The purpose of this study was to propose CMI as a new marker for cardiovascular risk, and thus ROC analysis and logistic regression analysis were performed for CMI. In addition, AUCs for CMI and other variables including waist circumference, BMI, triglycerides and LAP were compared as described above. A $p < 0.05$ was defined as significant.

3. Results

3.1. Profile of the subjects

Table 1 shows characteristics of the female and male subjects. The proportions of smokers, drinkers, subjects doing exercise regularly, those receiving therapy for diabetes, and those with hyperglycemia or diabetes were significantly higher in men than in women. Height, weight, waist circumference, BMI and WHtR were significantly larger or higher in men than in women. Triglycerides, TG/HDL-C ratio, hemoglobin A1c and CMI were also significantly higher in men than in women, while HDL cholesterol was significantly higher in women than in men.

3.2. Comparison of hemoglobin A1c levels among the four quartile groups of CMI

In both univariate and multivariate analyses, hemoglobin A1c was significantly higher in the highest quartile group of CMI than in the other lower quartile groups (Fig. 1). Hemoglobin A1c tended to be higher with an increase in the quartile of CMI. There were significant correlations between CMI and hemoglobin A1c in women and men (Pearson's correlation coefficient, 0.234 in women [$p < 0.01$] and 0.216 in men [$p < 0.01$]). In multiple regression of hemoglobin A1c on CMI with adjustment for age and histories of medication therapy for diabetes, smoking, alcohol drinking and regular exercise, standardized regression coefficients were also significant (0.228 in women [$p < 0.01$] and 0.195 in men [$p < 0.01$]).