Clinica Chimica Acta 446 (2015) 231–236

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/clinchim

Association between cardiometabolic index and atherosclerotic progression in patients with peripheral arterial disease

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ARTICLE INFO

Article history:
Received 16 February 2015
Received in revised form 16 April 2015
Accepted 18 April 2015
Available online 25 April 2015

Keywords:
Atherosclerosis
Cadiometabolic index
Cardiovascular disease
Lipid accumulation product
Peripheral arterial disease

ABSTRACT

Background: Cardiometabolic index (CMI), calculated as a product of waist-to-height ratio and triglycerides-to-HDL cholesterol ratio, is a new index for discriminating diabetes mellitus. Patients with peripheral arterial disease (PAD) are prone to have other atherosclerotic diseases such as coronary artery disease and stroke. The purpose of this study was to clarify the relationships between CMI and indicators of atherosclerotic progression in patients with PAD.

Methods: The subjects were 63 outpatients with PAD. Relationships of CMI with variables related to atherosclerotic progression were investigated using multivariate linear regression analysis and analysis of covariance with adjustment for age, sex and histories of smoking and alcohol drinking.

Results: Log-transformed CMI was significantly correlated with mean intima-media thickness of the common carotid artery (IMT) (standardized regression coefficient: 0.350, $p < 0.01$) and % decrease in ankle-brachial systolic pressure index (ABI) after treadmill exercise (standardized regression coefficient: 0.365, $p < 0.01$). Mean IMT and % decrease in ABI by treadmill exercise were significantly higher ($p < 0.01$) in the group of the 3rd tertile for CMI than in the group of its 1st tertile (mean ± SE: mean IMT (mm), 0.94 ± 0.06 (1st tertile) vs. 0.94 ± 0.06 (2nd tertile) vs. 1.19 ± 0.06 (3rd tertile); % decrease in ABI, 14.1 ± 3.4 [1st tertile] vs. 26.0 ± 3.5 [2nd tertile] vs. 30.0 ± 3.5 [3rd tertile]).

Conclusion: CMI was shown to be associated with the degrees of atherosclerosis in the common carotid artery and ischemia in leg arteries and is therefore a useful discriminator of atherosclerotic progression in patients with PAD.

1. Introduction

Peripheral arterial disease (PAD) is defined by the Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II) as atherosclerotic disease in the lower extremities [1] and is thus considered to have the same meaning as arteriosclerosis obliterans in the lower extremity arteries. Patients with PAD are prone to suffer from atherosclerotic diseases such as coronary artery disease and stroke [2,3]. In a previous study using subjects aged ≥70 y or aged 50 to 69 y with a history of cigarette smoking or diabetes, the prevalence of PAD was 29%, and 16% of the overall subjects had both PAD and atherosclerotic diseases (atherosclerotic coronary, cerebral or abdominal aortic aneurysmal disease) [4]. Thus, about 55% of the subjects with PAD also had other atherosclerotic disease. Therefore, in addition to therapy for PAD itself, prevention of and therapy for concomitant coronary artery disease and cerebrovascular disease are necessary to improve the prognosis for patients with PAD. Major risk factors for PAD are advanced age, smoking, diabetes mellitus, dyslipidemia and hypertension [1,5], which are also determinants for the risk of cardio- and cerebrovascular diseases.

Lipid accumulation product (LAP), calculated by using waist circumference and triglyceride level, has been proposed as a continuous marker of lipid over-accumulation [6]. LAP has been shown to be associated with cardiovascular events [6,7] and to predict all-cause mortality in nondiabetic patients at high risk for cardiovascular diseases [8]. LAP has also been reported to be a better discriminator for diabetes than body mass index (BMI), a general marker for obesity [9,10].

We have recently proposed cardiometabolic index (CMI) as a new discriminator for diabetes [11]. CMI showed strong associations with glycemic status evaluated by hemoglobin A1c in analysis of covariance (ANCOVA) and logistic regression analysis [11]. In comparison to LAP, CMI has the following merits. CMI includes waist circumference-to-height ratio (WHtR), a more reasonable index for abdominal obesity than waist circumference alone [12]. Waist circumference, a simple marker for visceral obesity, is often used as a component of metabolic syndrome [13]. WHtR, an index of waist circumference corrected by height, has been shown to be a better discriminator than waist circumference or BMI of cardiovascular risk factors and coronary artery disease [14–16]. HDL cholesterol, an important factor for determining

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http://dx.doi.org/10.1016/j.cca.2015.04.020
0009-8981/

cardiovascular risk [17], is also included in CMI. However, there have been no reports on the relationship between CMI and atherosclerotic disease.

Atherosclerosis is deeply involved in the pathogenesis of PAD, and diabetes is a major risk factor of PAD. CMI has been proposed as a new discriminator for diabetes and is a modified index of LAP [11], which has been reported to be a predictor of cardiovascular disease [6,7]. Therefore, it is of interest to know the relationships between CMI and markers of atherosclerotic progression in patients with PAD and to compare these relationships with the relationships between LAP and the markers. The purpose of this study was to determine whether CMI is related to the degree of atherosclerosis in PAD. The relationships of CMI with markers of atherosclerotic progression, including intima-media thickness of the common carotid artery (IMT), ankle-brachial systolic pressure index (ABI) and % decrease in ABI after exercise overload, were investigated in patients with PAD and were compared with the relationships of LAP with these markers.

2. Methods

2.1. Subjects

The subjects of this study were 63 outpatients (54 men and 9 women) with a mean age of 74.6 ± 7.9 y who had been diagnosed as having PAD defined as a low ankle-brachial systolic pressure index (ABI < 0.9) and/or a low toe-brachial systolic pressure index (TBI < 0.7) [1,18]. This study was approved by the Ethics Committee of Yamagata Saisei Hospital. Histories of illness, medication, cigarette smoking and alcohol consumption were surveyed by questionnaires. The subjects were divided into six groups by pack-year of cigarette consumption (nonsmokers, > 0 and ≤ 10, > 10 and ≤ 20, > 20 and ≤ 40, > 40 and ≤ 60, > 60).

2.2. Measurements

Waist circumference was measured at the navel level according to the recommendation of the Japanese Committee for the Diagnostic Criteria of Metabolic Syndrome [19]. Fasted blood was sampled from each subject in the morning. Serum triglyceride, HDL cholesterol and LDL cholesterol concentrations were measured by enzymatic methods using commercial kits, Determiner TG II, Metabolead HDL-C and Metabolead LDL-C (Kyowa Medex Co., Ltd.), respectively. The coefficients of variation for the reproducibility of measurement were ≤ 3% for triglycerides and ≤ 5% for HDL cholesterol and LDL cholesterol. CMI was calculated as a product of waist-to-height ratio and triglycerides-to-HDL cholesterol ratio [11]. LAP was determined by using triglyceride level (TG) and waist circumference (WC) as follows: LAP = TG (mmol/L) × (WC (cm) – 65) for men and LAP = TG (mmol/L) × (WC (cm) – 58) for women [6]. Hemoglobin A1c was measured by using an automatic glyco-hemoglobin analyzer based on high-performance liquid chromatography (ADAMS™ A1c HA-8170, Sekisui Medical Co., Ltd). The coefficient of variation for reproducibility of hemoglobin A1c measurement was ≤ 5%. Since the standards of hemoglobin A1c used for measurement are different in the NGSP (National Glycohemoglobin Standardization Program) method and the JDS (Japan Diabetes Society) method, hemoglobin A1c values were calibrated by using a formula proposed by the JDS [20]: hemoglobin A1c (NGSP) (%) = 1.02 × hemoglobin A1c (JDS) (%) + 0.25%. Subjects with diabetes were defined as those receiving drug therapy for diabetes and/or those showing high hemoglobin A1c levels (≥6.5%), according to the criteria for diagnosis of diabetes by the American Diabetes Association [21].

After each subject had rested quietly in a supine position, ABI was measured by an oscillometric method using an automatic ABI device (VaSera VS-1500, Fukuda Denshi) at rest and after stress loading. Two methods were used to load stress at the legs: one was exercise by a treadmill with a slope of 12% and a speed of 2.4 km/hr for 1 min, corresponding to 40 m walk [22], and the other was fatigue in gastrocnemius and soleus muscles induced by isotonic ankle plantar flexion exercise (100 pedals for each leg at 60 beats per minute in an alternate basis corresponding to 5.3 joules of work) using a leg loader (VSL-100A, Fukuda Denshi), a stress-loading device developed by Toribatake and Komine [23]. Mean values measured at the right and left legs were used for analysis of ABI and % decrease in ABI after stress loading. The exercises using leg loader and treadmill could not be performed by two and four subjects, respectively, because of the weak power of their leg muscles. Arterial pressure of the right brachial artery was also recorded using CAVI-Vasera VS-1500.

The intima-media thickness (IMT) of the common carotid arteries was measured by ultrasonography in the supine position. Well-trained sonographers scanned high-resolution B-mode ultrasound images (Philips CX50, PHILIPS Electronics Japan) with a L12-3 MHz transducer. Three arterial wall segments in each common carotid artery were imaged from a fixed lateral transducer angle at the far wall. Far wall IMT of both common carotid arteries was measured at three determinations (greatest thickness point and 1 cm-upstream and -downstream points from the greatest thickness point). Mean IMT over the 6 segments of both common carotid arteries was calculated and was designated mean IMT. Mean IMT < 1.0 mm was regarded as normal [24].

2.3. Statistical analysis

Statistical analyses were performed using a computer software program (SPSS ver 16.0 J). Data are presented as means ± standard deviations (SDs) or errors (SEs) for variables showing normal distributions and medians with 25 and 75 percentile values for variables not showing normal distributions. The values of CMI or LAP in subjects were arranged in ascending order, and then the subjects were divided into three tertile groups of equal sizes. Means of each variable were compared among the subject groups of the 1st, 2nd and 3rd tertiles for CMI or LAP by using ANCOVA followed by Student's *t*-test after Bonferroni correction. In linear regression analysis, Pearson's correlation coefficients and standardized regression coefficients were calculated. In multivariate analyses, age, sex, smoking and alcohol drinking were used as other explanatory variables or covariables. In some analyses, history of diabetes was also added to the explanatory variables or covariables. Since CMI and LAP did not show normal distributions, they were used for parametric analyses after logarithmic transformation. The Shapiro-Wilk test was used to evaluate a distribution for normality. Probability (p) values less than 0.05 defined as significant.

3. Results

The characteristics of the subjects are shown in Table 1. Their mean age was 74.6 y (56–91 y), and about three-fourths of the subjects were ≥70 y. The proportion of smokers was high (85.7%), and about half of the subjects were drinkers. Thirty percent of the subjects had diabetes. The mean level of mean IMT was 1.02 mm, and 50.8% of the subjects showed high mean IMT (≥1.0 mm). The mean ABI was 0.910, and 34.9% and 41.3% of the subjects showed low levels of ABI (<0.900) and borderline levels of ABI (<1.000 and ≥ 0.900), respectively. The decrease in ABI after treadmill exercise was greater than that after leg loader exercise (23.1% vs. 12.2%).

Histograms for CMI and log-transformed CMI are presented in Fig. 1. *W* values for CMI and log-transformed CMI in the Shapiro-Wilk test were 0.916 ($p < 0.001$) and 0.977 ($p = 0.293$), respectively. Thus, CMI itself did not show a normal distribution but showed a normal distribution after logarithmic transformation. The cut-off value of CMI for discriminating diabetes has been reported to be 1.748 for men [11]. In the present study, median CMI was 0.978 in men, and 13.0% of the male subjects showed CMI values higher than 1.748.

Table 2 shows Pearson's correlation coefficients between each variable and log-transformed CMI or LAP. Log-transformed CMI showed