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Association of cardio-ankle vascular index with cardiovascular risk factors and cardiovascular events in metabolic syndrome patients

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ABSTRACT

Objectives: We aimed to investigate the association between arterial stiffness assessed as cardio-ankle vascular index (CAVI) and cardiovascular (CV) risk factors and CV events in the middle-aged metabolic syndrome (MS) patients.

Materials and methods: A follow-up study was carried out in 2106 middle-aged (53.83 ± 6.17 years old, 62% women) MS subjects without overt atherosclerotic disease. Patients were initially recruited in 2009–2011 as participants of the Lithuanian High Cardiovascular Risk (LitHiR) primary prevention program and followed up for 3.8 ± 1.7 years for CV events. Thorough cardiometabolic risk assessment was carried out at inclusion.

Results: Subjects with higher CAVI had worse lipid and glucose metabolism profile: elevated total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C), decreased high-density lipoprotein cholesterol (HDL-C), higher fasting and oral glucose tolerance test (OGTT) glucose levels (all $P < 0.001$), and lower fasting insulin ($P = 0.021$). Greater age ($P < 0.001$), heart rate ($P = 0.016$), and mean arterial pressure ($P < 0.001$) were also associated with higher CAVI. Over the follow-up period, 93 (4.4%) patients developed a cardiovascular event: 55 (2.6%) patients had myocardial infarction and 38 (1.8%) suffered a cerebrovascular event. Fatal CV events comprised 6.5% ($n = 6$) of all CV events. CAVI was statistically significantly associated with occurrence of myocardial infarction ($P = 0.027$) and total cardiovascular events ($P = 0.045$), but not cerebrovascular events ($P = 0.65$). However, this association was dependent on age and gender.

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Conclusions: In the middle-aged MS patients, higher CAVI was associated with altered lipid and glucose metabolism, older age, greater heart rate and mean arterial pressure, and worse cardiovascular outcome.

1. Introduction

Metabolic syndrome (MS) is a complex of cardiovascular (CV) risk factors such as impaired glucose tolerance, high blood pressure, dyslipidemia and abdominal obesity [1,2]. Patients with MS also frequently manifest a prothrombotic and proinflammatory state [3], therefore MS is considered to be a chronic inflammatory condition [4]. Almost one-quarter of the world's adult population already have MS [5], which accounts for a 2-fold increase in the risk of developing cardiovascular disease [6]. Moreover, MS is associated with impaired arterial stiffness [7], which has an independent predictive value for all-cause and CV mortality [8]. Therefore, it is believed that early evaluation of arterial stiffness might prevent future cardiovascular events in patients with MS. However, data on the predictive value of blood pressure-independent arterial stiffness index CAVI for cardiovascular events in MS patients are not available.

Aortic pulse wave velocity (PWV) is considered to be the ''gold standard'' for measuring arterial stiffness [9]. Furthermore, recent meta-analysis of 17 longitudinal studies has shown that PWV is a predictor of cardiovascular events and all-cause mortality in various populations [10]. In pre-diabetic and diabetic patients, the value of PWV as an integrated index of vascular function predicting mortality was first shown by Cruickshank et al. [11]. However, the major limitation to clinical usage of the PWV is its dependence on blood pressure during measurement [12].

Recently, another arterial stiffness parameter, the cardio-ankle vascular index (CAVI), has been developed. CAVI reflects the stiffness of the aorta, femoral and tibial artery, and it can be assessed simultaneously with ankle-brachial index by a non-invasive VaSera device (Fukuda Denshi Co., Tokyo, Japan) [13]. Contrary to PWV, CAVI is essentially independent of blood pressure at measuring time [14–16] because it is calculated by Bramwell–Hill equation, which corrects for blood pressure parameters [12]. Consequently, CAVI represents both 'functional' and 'organic' arterial stiffness [17] and reflects both the state of smooth muscle contraction and mechanical properties of the arterial wall [18]. Moreover, CAVI enables evaluation of the real effect of blood pressure control on arteries during antihypertensive therapy [12,19]. These theoretical presuppositions and first findings of the clinical studies [20,21] support the assertion that CAVI might be equal or superior to PWV as a long-term CV risk predictor.

Several studies have investigated the association between the new index of arterial stiffness CAVI and MS. Satoh et al. [22] reported that CAVI values were significantly higher in MS than in non-MS patients. Liu et al. [23] demonstrated that CAVI increased with the number of MS components. However, there have been no large population-based studies on the association of various CV risk factors and CAVI in MS patients, and, to our best knowledge, there is no follow-up study reporting the association of CAVI and CV outcome in MS patients. In addition, most of the aforementioned studies were done on Asian populations.

Hence, the objective of this study was to evaluate the association of CAVI with traditional CV risk factors and with CV events in middle-aged MS patients.

2. Materials and methods

2.1. Subjects and study design

A follow-up study was carried out among 2106 MS subjects without overt atherosclerotic disease. All patients were recruited between 2009 and 2011 as participants of the Lithuanian High Cardiovascular Risk (LitHiR) primary prevention program, which enrolled employable age women (aged 50–65 years) and men (aged 40–55 years) without prior history of CV disease as described previously [24]. Our study cohort was comprised of the LithHir patients admitted to the Vilnius University Hospital Santariškių Klinikos (VUHSK) with diagnoses of MS according to the revised National Cholesterol Education Program Adult Treatment Panel III (NCEP ATPIII) criteria [25].

Data on the fatal and non-fatal cardiovascular events (myocardial infarction, stroke or transient ischemic attack, and sudden cardiac death) were obtained after a follow-up period greater than 3 years. The outcome follow-up was carried-out by submitting an inquiry about CV events to the National Death Registry and National Healthcare Fund Disease and Services Database. The outcome data were retrieved in June 2014.

The study was approved by the Regional Ethics Committee (Permission No. 158200-13-641-205).

2.2. Baseline measurements

All patients underwent detailed assessment of the physical status, anthropometry, and CV risk profile, including height, weight, waist circumference, and body mass index (BMI) measurements and evaluation of the CV risk factors (smoking, positive family history of CV disease). BMI was calculated as weight in kilograms divided by height in meters squared. Smoking was recorded if the subject smoked at least one cigarette a day. Positive CVD family history was defined as

having a first-degree relative with any CV event at young age (men ≤ 45 years, women ≤ 55 years old). In all patients 12 lead electrocardiogram, blood pressure and heart rate were registered. Blood pressure was measured twice on the right arm with oscillometric semiautomatic device (Schiller Argus VCM) with a standard bladder (12–13 cm long and 35 cm wide), validated according to standardized mercury sphygmomanometer, after the participant had been resting for at least 5 min. Mean arterial pressure (MAP) was calculated by the equation: MAP = [(2 × diastolic pressure) + systolic pressure]/3.

After a 12-h fast, venous blood sample was collected for assessment of serum total cholesterol (TC), low density lipoprotein (LDL-C) cholesterol, high density lipoprotein (HDL-C) cholesterol, triglycerides (TG), and high sensitivity C-reactive protein (hsCRP). Both fasting plasma glucose and insulin and glucose and insulin after oral glucose tolerance test (OGTT) were sampled, and insulin resistance indices were calculated. The Homeostasis Model Assessment Insulin Resistance Index (HOMA-IR) was calculated as $\text{Insulin}_{\text{fasting}}[\mu\text{U/ml}] \times \text{Glucose}_{\text{fasting}}[\text{mmol/l}]/22.5$ [26]. Insulin sensitivity index ISI-Matsuda was calculated as $10{,}000/[\text{SQR}(\text{Glucose}_{\text{fasting}} \times \text{Insulin}_{\text{fasting}}) \times (\text{Glucose}_{\text{OGTT mean}} \times \text{Insulin}_{\text{OGTT mean}})]$ [27].

Arterial stiffness indices were obtained for each patient by VaSera-1000 device (Fukuda Denshi Co. Ltd., Tokyo, Japan). According to the specification of the device, measurements on the right and the left side of the body (right CAVI and left CAVI) were obtained, and the mean CAVI was calculated for major statistical analysis. Blood pressure cuffs with sensors were wrapped around both ankles and upper arms to register plethysmograms. Electrocardiographic electrodes were attached to the upper arms and a phonocardiogram (PCG) was placed at the right sternal border in the 2nd intercostal space. After having the subjects rest for 10 min in a supine position and the head held in midline position, the examinations were performed. All measurements were calculated automatically by the following formula:

$$\text{CAVI} = a\left\{\left(\frac{2\rho}{\Delta P}\right) \times \ln\left(\frac{P_s}{P_d}\right)\text{PWV}^2\right\} + b$$

where P_s and P_d are systolic and diastolic blood pressure values, respectively, PWV is the pulse wave velocity between heart and ankle, ΔP is pulse pressure, ρ is blood density and a, b are constants.

2.3. Statistical analysis

Descriptive statistics are presented as mean and standard deviation for the continuous variables and as counts and frequencies for the categorical variables. Differences between groups were analyzed by unpaired Student's t test (continuous variables with normal distribution), nonparametric tests (continuous variables with skewed distribution), Pearson chi-square test (categorical variables), and by Cox proportional hazard regression analysis. Kaplan–Meier survival curves were constructed for comparison of the cumulative proportion of the event-free survival in subjects with CAVI above and below the median. Statistical analysis was performed with STATISTICA (StatSoft, version 10). In all comparisons, values of $P < 0.05$ were considered statistically significant.

3. Results

3.1. Baseline characteristics

Out of 2106 subjects enrolled in the study, there were 1307 (62%) women and 799 (38%) men. The characteristic of the entire study population and of the subgroups by gender is presented in Table 1. Men and women differed by majority of the variables measured, and the left CAVI, but there was no statistically significant difference in terms of mean CAVI ($P = 0.098$), a comprehensive index of arterial stiffness.

3.2. Relation of low and high CAVI values to CV risk factors

The median of CAVI for our cohort (both men and women) was 7.95. CAVI above the median was more frequent among the women ($n = 691$, 54%) as compared to men ($n = 346$, 44%) ($P < 0.0001$). Subjects with CAVI above and below the median did not differ significantly by the frequency of smoking ($P = 0.74$), diabetes ($P = 0.25$), family CV disease history ($P = 0.72$), and presence of the central obesity ($P = 0.23$).

In a univariate analysis, subjects with higher CAVI had worse lipid and glucose metabolism profile: CAVI above the median was statistically significantly associated with abnormal levels of TC, LDL-C, and HDL-C, higher fasting and OGTT glucose levels (all $P < 0.001$), and lower fasting insulin ($P = 0.021$) (Table 2). However, TG ($P = 0.891$) and insulin resistance and sensitivity indices did not differ significantly between low and high CAVI groups. Subjects with high CAVI values also were older ($P < 0.001$) and had higher heart rate ($P = 0.016$) and mean arterial pressure ($P < 0.001$).

In order to adjust for gender and age, eight logistic regression models were constructed. CAVI level below or above the median was included as dependent variable, whereas gender, age and each of CV risk factor, which was statistically significantly associated with the presence of high CAVI in the univariate analysis (Table 2), was included as independent variables. Total cholesterol ($P = 0.043$), fasting glucose ($P < 0.007$), heart rate ($P < 0.01$), and mean arterial pressure ($P < 0.001$) remained significantly associated with the presence of CAVI above the median even after adjustment for age and gender.

3.3. Follow-up data

The duration of the follow-up was 3.8 ± 1.7 years. Over the follow-up period, 93 (4.4%) patients developed a cardiovascular event: 55 (2.6%) patients had myocardial infarction and 38 (1.8%) suffered a cerebrovascular event. Fatal CV events comprised 6.5% ($n = 6$) of all CV events, and there were 2 deaths due to cancer.

The comparison of CAVI between the CV event and CV event-free groups (Table 3) demonstrated that mean CAVI was statistically significantly associated with occurrence of all cardiovascular events ($P = 0.045$) and myocardial infarction ($P = 0.027$), but not cerebrovascular events ($P = 0.651$). Univariate analysis has also shown that subjects in the CV event

Table 1 – Baseline characteristics of the participants.

Variable	All subjects	Women	Men	P*
Age, years	53.83 ± 6.17	57.39 ± 4.08	48.02 ± 4.31	<0.001
Height, m	1.68 ± 0.10	1.61 ± 0.06	1.78 ± 0.07	<0.001
Weight, kg	90.66 ± 17.07	84.19 ± 14.23	101.25 ± 16.01	<0.001
BMI, kg/m^2	32.20 ± 4.89	32.29 ± 5.19	32.06 ± 4.34	0.283
Waist circumference, cm	107.08 ± 10.80	104.77 ± 10.58	110.87 ± 10.08	<0.001
TC, mmol/L	6.98 ± 1.54	7.12 ± 1.40	6.75 ± 1.71	<0.001
LDL-C, mmol/L	4.51 ± 1.29	4.74 ± 1.25	4.14 ± 1.26	<0.001
HDL-C, mmol/L	1.26 ± 0.34	1.35 ± 0.30	1.11 ± 0.34	<0.001
TG, mmol/L	2.66 ± 2.69	2.22 ± 1.29	3.37 ± 3.94	<0.001
Fasting glucose, mmol/L	6.26 ± 1.31	6.16 ± 1.16	6.44 ± 1.50	<0.001
Plasma glucose after OGTT, mmol/L	6.66 ± 2.45	7.12 ± 2.56	5.94 ± 2.06	<0.001
Plasma fasting insulin, pmol/L	100.40 ± 61.75	93.66 ± 60.37	111.14 ± 62.44	<0.001
Plasma insulin after OGTT, pmol/L	385.39 ± 329.04	421.57 ± 324.89	330.32 ± 328.01	<0.001
HbA1c, %	5.98 ± 0.69	5.97 ± 0.59	5.99 ± 0.82	0.337
Right CAVI	7.98 ± 1.51	8.00 ± 1.41	7.95 ± 1.66	0.430
Left CAVI	7.86 ± 1.53	7.91 ± 1.39	7.76 ± 1.72	0.030
Mean CAVI	7.92 ± 1.43	7.96 ± 1.35	7.85 ± 1.54	0.098
hsCRP, mg/dL	3.50 ± 4.76	3.51 ± 4.84	3.49 ± 4.62	0.926
Heart rate, bpm	65.87 ± 9.31	65.34 ± 9.16	66.73 ± 9.51	0.009
MAP, mmHg	108.31 ± 13.17	107.85 ± 13.22	109.07 ± 13.06	0.047
ISI-Matsuda, score	5.61 ± 6.07	5.37 ± 6.81	5.99 ± 4.71	0.095
HOMA-IR, score	4.20 ± 3.44	3.87 ± 3.23	4.71 ± 3.68	<0.001
Smoking, *n* (%)	513 (24)	188 (14)	325 (41)	<0.001
Family history of CVD, *n* (%)	723 (34)	448 (34)	275 (35)	0.920
Diabetes, *n* (%)	394 (19)	245 (19)	149 (19)	0.960

Values are mean ± standard deviation unless otherwise indicated.
BMI, body mass index; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; OGTT, oral glucose tolerance test; HbA_{1c}, glycated hemoglobin; CAVI, cardio-ankle vascular index; hsCRP, high sensitivity C-reactive protein; MAP, mean arterial pressure; HOMA-IR, homeostasis model assessment of insulin resistance index; ISI-Matsuda, Matsuda insulin sensitivity index; CVD, cardiovascular disease.
* *P* value is provided for comparison between men and women.

group as compared to the event-free group were older (55.3 ± 5.9 vs. 53.8 ± 6.2, $P = 0.017$) and had slightly higher fasting glucose levels (6.54 ± 1.51 vs. 6.25 ± 1.30, $P = 0.049$), but did not differ by other variables.

Cox proportional hazard regression analysis showed that an increase in the mean CAVI by one standard deviation is associated with a 26% increase in cardiovascular event risk (HR = 1.26; 95% CI, 1.03–1.55; $P = 0.026$). However, when all

Table 2 – The comparison between CV risk factors and CAVI values below and above the median.

Variable	CAVI value below the median	CAVI value above the median	P*
Age, years	52.23 ± 6.07	55.36 ± 5.92	<0.001
TC, mmol/L	6.88 ± 1.56	7.07 ± 1.51	0.004
LDL-C, mmol/L	4.42 ± 1.29	4.59 ± 1.28	0.004
HDL-C, mmol/L	1.28 ± 0.33	1.23 ± 0.34	0.004
TG, mmol/L	2.66 ± 2.55	2.68 ± 2.86	0.860
Fasting glucose, mmol/L	6.20 ± 1.18	6.34 ± 1.44	0.023
Plasma glucose after OGTT, mmol/L	6.51 ± 2.30	6.81 ± 2.58	0.031
Plasma fasting insulin, pmol/L	104.22 ± 69.08	97.07 ± 54.15	0.021
Plasma insulin after OGTT, pmol/L	371.72 ± 307.32	396.41 ± 345.19	0.198
HbA1c, %	5.96 ± 0.67	6.00 ± 0.71	0.201
hsCRP, mg/dL	3.69 ± 4.95	3.32 ± 4.60	0.083
Heart rate, bpm	65.40 ± 9.05	66.48 ± 9.57	0.040
MAP, mmHg	107.00 ± 12.91	109.30 ± 13.21	<0.001
ISI Matsuda, score	5.72 ± 6.34	5.53 ± 5.90	0.592
HOMA-IR, score	4.28 ± 3.44	4.14 ± 3.48	0.408

Values are mean ± standard deviation.
BMI, body mass index; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; OGTT, oral glucose tolerance test; HbA_{1c}, glycated hemoglobin; CAVI, cardio-ankle vascular index; hsCRP, high sensitivity C-reactive protein; MAP, mean arterial pressure; ISI-Matsuda, Matsuda insulin sensitivity index; HOMA-IR, homeostasis model assessment of insulin resistance index.
* Student's *t* test, age and gender unadjusted.

Table 3 – The association between CV events and CAVI.

	CV event –	CV event +	P*
All CV events			
Right CAVI	7.96 ± 1.52	8.33 ± 1.27	0.024
Left CAVI	7.84 ± 1.53	8.09 ± 1.52	0.136
Mean CAVI	7.90 ± 1.43	8.21 ± 1.31	0.045
Fatal or non-fatal MI			
Right CAVI	7.97 ± 1.52	8.33 ± 1.35	0.085
Left CAVI	7.84 ± 1.52	8.34 ± 1.59	0.017
Mean CAVI	7.90 ± 1.42	8.33 ± 1.43	0.027
Cerebrovascular events			
Right CAVI	7.97 ± 1.52	8.32 ± 1.16	0.159
Left CAVI	7.86 ± 1.53	7.72 ± 1.35	0.569
Mean CAVI	7.91 ± 1.43	8.02 ± 1.09	0.651

Values are mean ± standard deviation.
CAVI, cardio-ankle vascular index; MI, myocardial infarction.
* Student's *t* test, age and gender unadjusted.

variables significant in the univariate analysis were included into the Cox proportional hazard regression model, gender (HR = 2.77; 95% CI, 1.49–5.14, $P = 0.001$) and age (HR = 1.74; 95% CI, 1.27–2.38, $P < 0.001$), but not the mean CAVI (HR = 1.12; 95% CI, 0.9–1.4; $P = 0.302$) and fasting glucose (HR = 1.16; 95% CI, 0.98–1.39; $P = 0.085$) remained to be associated with the occurrence of the cardiovascular event.

In Kaplan–Meier analysis, CAVI above median was statistically significantly ($Z = 2.079$, $P = 0.038$) associated with better CV event-free survival (Figure).

4. Discussion

In this large follow-up study, the association of CAVI with traditional CV risk factors in middle-aged Lithuanian patients with MS was evaluated. We demonstrated that elevated CAVI was statistically significantly associated with elevated total and low-density lipoprotein cholesterol, decreased high-density lipoprotein cholesterol, higher fasting and OGTT glucose levels, and lower fasting insulin, greater age, heart rate, and mean arterial pressure. Though previous studies [16,28], which examined healthy subjects, found gender-related differences of CAVI index, we did not observe statistically significant gender-related difference. The latter result can be explained by the fact that LitHir study enrolled men and women of a similar CV risk (women were older than men). The difference in age between men and women in our study, however, limits our potential to analyze gender-related CAVI differences in MS patients.

The association of dyslipidemia and CAVI has been widely investigated, but not among MS patients. CAVI was reported to be increased among dyslipidemic patients in comparison with healthy subjects [29]. Moreover, Takaki noted that CAVI is related to the total cholesterol/HDL-C ratio and to the LDL-C level [30]. Another study has investigated patients with abnormal HDL-C level, which was associated with significantly higher CAVI ($P < 0.01$) [23]. In addition, Satoh et al. showed the correlation between elevated CAVI and abnormal TG and HDL-C, especially in men [22]. Lipid-lowering agents such as pitavastatin [31] and eicosapentaenoic acid were reported to improve CAVI [32]. However, some studies stated that dyslipidemia was not associated with CAVI [28,33]. Our study confirmed significant associations between an elevated CAVI index and abnormal levels of TC, LDL-C, and HDL-C, except for TG, in MS patients.

Impaired fasting glucose level was reported to be another independent risk factor for increased CAVI, mostly in patients with diabetes [12,34]. Furthermore, it was demonstrated that lowering the blood glucose level with insulin therapy decreases CAVI in a relatively short period [28]. Consequently, CAVI has been proposed to be an additional parameter, which may reflect the status of diabetes control [18]. Ibata et al. noted

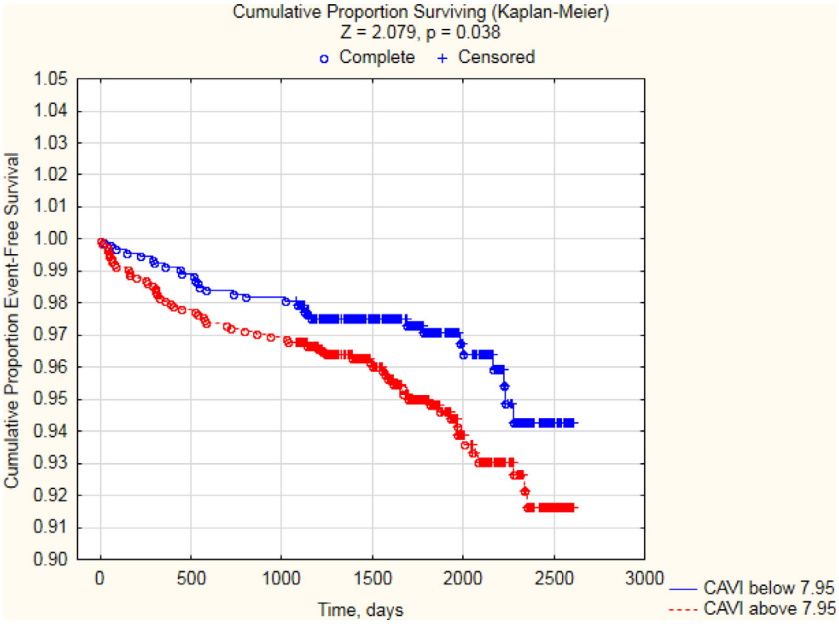

Figure – Kaplan–Meier curves for CV event-free survival in high and low CAVI groups.

that mild glucose intolerance may be associated with the increased arterial stiffness in MS patients as well [14]. In our MS subjects, higher CAVI values were significantly associated with increased fasting and OGTT glucose levels, but we did not demonstrate an association between CAVI and insulin resistance and sensitivity indices, thus suggesting that glycaemia per se has the greatest impact on the arterial wall.

We did not observe a significant relationship between higher CAVI scores and elevated waist circumference, which, at first glance, contradicts some findings from previous studies [22,23]. Liu et al. reported that CAVI was significantly higher in subjects with abnormal waist circumference compared to normal subjects ($P < 0.01$) [23]. It has been reported that reducing weight is important for improving CAVI [35,36], and even short-term weight reduction may reliably decrease CAVI values ($P = 0.015$) [22]. Thus, the absence of the association between the presence of central obesity and magnitude of CAVI in MS, which is observed in our study, needs to be confirmed in other studies analyzing subjects with MS. A potential interpretation of such finding could be that the high prevalence of central obesity (92%) in our group is responsible for blunting the difference.

There is limited information on how elevated heart rate affects CAVI value in MS patients. Wang et al. observed that heart rate was independently associated with CAVI in hypertensive and healthy subjects [37]. We also found an association between an increased heart rate and higher CAVI scores.

In the follow-up we study, we showed that MS subjects with higher CAVI values have greater frequency of total CV events and myocardial infarction. The frequency of the cerebrovascular events exhibited a similar trend, but it did not reach statistical significance. Though the Cox proportional hazard regression model showed that CAVI did not remain an independent predictor of CV events, when age and gender are included into analysis, our result suggests that CAVI might be considered as a surrogate marker of the CV risk. Though data on the predictive value of CAVI in MS patients was not previously available, our study is consistent with findings in other populations. Otsuka et al. demonstrated the predictive value of CAVI for CV outcomes in patients with coronary heart disease ($P < 0.01$) [38]. Patients having ischemic changes on ECG or undergoing percutaneous transluminal coronary angioplasty were also found to have a higher CAVI index [12]. However, we were first to demonstrate that CAVI is associated with CV risk in MS patients.

Hence, the novelty of our study consists in providing large cohort data on the relationship of CAVI with various risk factors and, for the first time, demonstrating an association between relatively new arterial stiffness measure CAVI and frequency of cardiovascular events in MS subjects.

5. Conclusions

In conclusion, our study demonstrated the relationship between increased CAVI and elevated total and low-density lipoprotein cholesterol, decreased high-density lipoprotein cholesterol, higher fasting and OGTT glucose levels, and lower fasting insulin level. CAVI above the median was also associated with greater age, heart rate, and mean arterial pressure. Moreover, presence of the elevated CAVI in our study was associated with higher frequency of total cardiovascular events and myocardial infarction. This suggests that, in MS patients, CAVI may be considered as a surrogate CV risk marker.

Conflict of interest

The authors state no conflict of interest.

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