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Carotid intima-media thickness correlated with age and pulse wave velocity in ANCA-associated vasculitis patients

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ABSTRACT

Objective: Cardiovascular diseases are the main causes of mortality in the anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) patients. Carotid intima-media thickness (CIMT) measurement and pulse wave velocity (PWV) were performed to determine atherosclerosis and arterial stiffness as cardiovascular risk markers.

Patients and Methods: The data of 31 patients with AAV were compared with 21 healthy controls. Demographic and laboratory findings were recorded.

Results: Seventeen patients (54.8%) were male. Mean age was 52.6±11.5 years. CIMT was higher in the patient group [0.74 (0.65 – 0.84) vs 0.63 (0.57-0.74) mm; p=0.048]. PWV [7.9 (6.7-9.3) vs 7.8 (6.8-8.5) m/s; p=0.295] and augmentation index (AI) [22.5 (11.0-30.0) vs. 23 (9.5-30.5) mm/Hg, p=0.801] were similar in both groups. CIMT was correlated with age (r: 0.538, p<0.001) and PWV (r: 0.554 p< 0.001) while there was no correlation with AI (r: 0.047, p= 0.764).

Conclusion: The present study showed that CIMT is significantly increased and correlated with age and PWV in patients with AAV compared to controls. CIMT can be used as a screening tool as part of patient follow-up to identify patients at cardiac risk.

Keywords: ANCA-associated vasculitis, Cardiovascular risk, Carotid intima media thickness, Pulse wave velocity

1. INTRODUCTION

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a group of diseases characterized by inflammation of small vessels which may affect the cardiovascular system. The cardiovascular (CV) system is rarely involved in AAV, however it is associated with poor prognosis when present. A significant number of patients undergo major CV events and CV disease is still the leading cause of death after the first year [1,2]. Therefore, we need to monitor and diagnose patients at risk for CV disease at an early stage.

Arterial stiffness is associated with CV disease and may indicate the early phase of atherosclerosis regardless of symptoms [3]. We used pulse wave velocity (PWV) and augmentation index (AI) to assess arterial stiffness. Pulse wave analysis is a non invasive and an easy diagnostic tool for assessing arterial stiffness [4]. Likewise, increased carotid artery intima-media thickness (CIMT), correlates with severity of coronary atherosclerosis and cardiovascular risk [5]. Therefore, arterial stiffness and CIMT may predict atherosclerosis before clinically overt CV disease develops and may help clinicians reduce CV disease related morbidity and mortality.

In the current study, we investigated CIMT and PWV for detecting subclinical cardiovascular disease in patients with AAV.

2. PATIENTS and METHODS

Study population

The study conforms with the Declaration of Helsinki and was approved by the Marmara University, School of Medicine, Ethics Committee (date/no: 2018/09.2018.653). Written informed consent was obtained from all participants.

Patients were followed up at the nephrology outpatient clinic where the study was conducted. Thirty-one AAV patients

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and 21 sex and age-matched controls were enrolled. Patients were excluded if they were known to have valvular heart disease, coronary artery disease, cardiomyopathy, heart failure, arrhythmia, peripheral arterial disease, poor echogenicity, end-stage chronic renal disease or malignancy. Demographic data and medical history including disease duration, disease activity, damage scores, current and past cumulative doses immunosuppressive treatments were recorded. Complete blood count and biochemistry tests were done following a 12-hour fasting period.

Assessment of CIMT

Carotid intima media thickness was measured by Vivid 7, GE Vingmed Ultrasound AS, Horten, Norway echocardiography/ultrasonography system provided with a 10 MHz linear transducer. The same operator blindly performed all of the measurements. CIMT was measured from the first echogenic line to second echogenic line bilaterally at the common carotid artery bifurcation. The longitudinal view of the far wall of the distal common carotid arteries was used during the diastolic phase. CIMT was calculated as mean of three measurements on each side. If a plaque existed, no measurement was carried out on these sites.

Assessment of arterial stiffness parameters

Arterial stiffness was assessed after a fasting of 12 hours in all subjects in the supine position in a temperature controlled room (22-24°C). PWV and AI were measured according to current guidelines by a Mobil-O-Graph arteriography system (Mobil-O-Graph NG, Stolberg, Germany) which detects signals from the brachial artery. PWV and AI were adjusted for a heart rate of 75 bpm.

Statistical Analysis

SPSS (version 22.0; SPSS Inc, Chicago, IL) statistics package was used for statistical analysis. Categorical variables were presented as numbers and percentages and compared with the Chi-square test. Continuous variables were presented as mean ± standard deviation. Continuous variables with parametric distribution were compared with independent samples t-test and those without normal distribution were compared with Mann-Whitney U-test. Kolmogorov-Smirnov or Shapiro Wilk tests were performed to determine whether continuous variables were normally distributed. According to the normality tests, those with $p \geq 0.05$ were considered to be normally distributed. Spearman's correlation analysis performed for correlation analysis between CIMT, PWV and AI. For all statistical analyses, a p-value <0.05 was considered significant.

3. RESULTS

The study population included 31 patients with AAV and 21 controls. Twenty patients (64.5%) had a diagnosis of granulomatosis with polyangiitis (GPA) and 11 patients (35.5%) had a diagnosis of microscopic polyangiitis (MPA). Thirteen patients (41.9%) were positive for perinuclear (p)-ANCA and 18 (58.1%) were positive for cytoplasmic (c)-ANCA at diagnosis. The echocardiographic findings of the patient cohort have been reported previously [6]. The demographic and laboratory data are shown in Table I. There was no difference in sex and age among the study groups. Mean patient age was 52.6±11.5 years and 17 (54.8%) of the patients were male. Duration of disease was 36 months (18-91 months). Frequency of hypertension (HT) [14 (45.2%) vs. 1 (4.8%), p= 0.001] and mean systolic blood pressure [133.4 ± 17.9 vs. 120.9 ± 12.7, p= 0.008] were significantly higher in patients with AAV compared with controls. Serum triglyceride (204.06 ± 11.92 vs. 128.30 ± 102.67 mg/dl, p=0.019), creatinine (1.36 ± 0.71 vs. 0.71±0.17 mg/dl, p< 0.001) and C-reactive protein (CRP) (7.16 ± 9.03 vs. 3.50 ± 0.70 mg/L, p= 0.032) levels were significantly higher in patients compared with controls.

Table I. *The clinical and biochemical characteristics of the study populations.*

	Patients n:31	Controls n:21	P
Age, years	52.6 ± 11.5	51.9 ± 12.1	ns
Male gender, n (%)	17 (54.8%)	11 (52.4%)	ns
BMI, kg/m^2	28.4 ± 17.3	27.4 ± 3.4	ns
Hypertension, n (%)	14 (45.2%)	1 (4.8%)	0.001
Systolic blood pressure, mmHg	133.4 ± 17.9	120.9 ± 12.7	0.008
Diastolic blood pressure, mmHg	85.9 ± 15.1	79.4 ± 9.9	ns
Diabetes mellitus, n (%)	4 (12.9%)	1 (4.8 %)	ns
Birmingham vasculitis activity score	2.77 ± 1.94		
Vasculitis damage index	2.23 ±1.50		
Current steroid use, n (%)	15 (48.4%)		
Current azathioprine use, (%)	14 (45.2%)		
Current methotrexate use, (%)	2 (6.5%)		
Current rituximab use, (%)	15 (48.4%)		
Cumulative steroid dose, mg	10518 ± 7545		
Cumulative cyclophosphamide dose, mg	11852 ± 48445		
Cumulative azathioprine dose, mg	112994 ± 145068		
Cumulative rituximab dose, mg	3936 ± 4328		
Glucose, mg/dl	91.6 ± 15.4	92.5 ± 10.2	ns
Creatinine, mg/dl	1.36 ± 0.71	0.71 ± 0.17	<0.001
Total cholesterol, mg/dl	233.52±55.25	202.15±47.30	ns
LDL cholesterol, mg/dl	139.74 ± 42.05	122.74 ± 39.96	ns
HDL cholesterol, mg/dl	53.52 ± 14.71	55.05 ± 16.31	ns
Triglyceride, mg/dl	204.06 ± 11.92	128.30 ± 102.67	0.019
CRP (mg/L)	7.16 ± 9.03	3.50 ± 0.70	0.032

ANCA: Anti-neutrophil cytoplasmic antibody; **BMI**: Body mass index; **c-ANCA**: Cytoplasmic: Anti-neutrophil cytoplasmic antibody; **CRP**: C reactive protein; **HDL**: High density lipoprotein; **LDL**: Low density lipoprotein; **p-ANCA**: Perinuclear anti-neutrophil cytoplasmic antibody. ns: non significant

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Carotid artery intima-media thickness was significantly higher in AAV patients [0.74 (0.65-0.84) vs. 0.63 (0.57-0.74), p=0.048], however, PWV pulse wave velocity [7.9 (6.7-9.3) vs. 7.8 (6.8-8.5) m/s, p=0.295] and AI [22.5 (11.0-30.0) vs. 23 (9.5-30.5) mm/Hg, p=0.801] were similar in both groups (Table II). CIMT was correlated with age (r: 0.538, p< 0.001) and PWV (r: 0.554 p< 0.001) while there was no correlation with AI (r: 0.047, p= 0.764) (Figure 1 and 2).

Table II. *Comparison of carotid intima-media thickness, pulse wave velocity and augmentation index between AAV patients and controls.*

	Patients n: 31	Controls n: 21	P
Carotid intima-media thickness, cm	0.74 (0.65-0.84)	0.63 (0.57-0.74)	0.048
Pulse wave velocity, m/s	7.9 (6.7-9.3)	7.8 (6.8-8.5)	ns
Augmentation index, mmHg	22.5 (11.0-30.0)	23.0 (9.5-30.5)	ns
ns: Non significant			

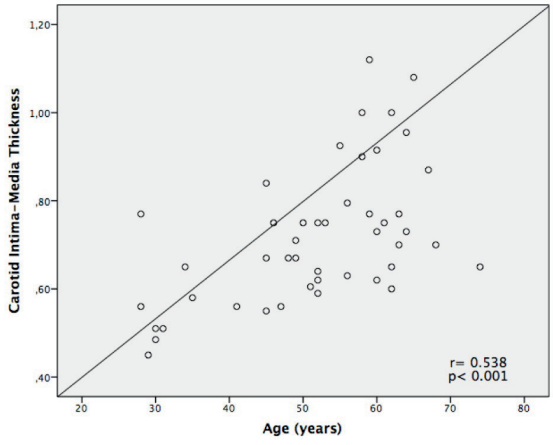

Figure 1. *Correlation analysis between carotid intima-media thickness and age*

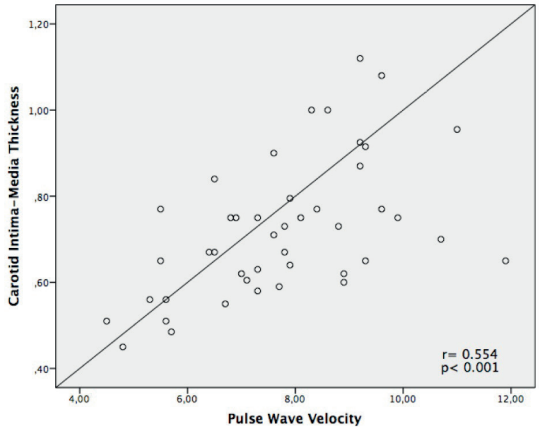

Figure 2. *Correlation analysis between carotid intima-media thickness and pulse wave velocity*

4. DISCUSSION

The main finding of the present study is that CIMT is significantly increased and correlated with age and PWV in patients with AAV compared to controls. Arterial stiffness, as assessed by PWV and AI, was similar in both groups. Despite the fact that cardiovascular disease is one of the most common causes of mortality in AAV patients, overt cardiac disease is rare [7,8]. On the other hand, AAV is characterized by vascular inflammation which can cause endothelial dysfunction, leading to subclinical atherosclerosis [9,10].

In our study, we found that CIMT was higher in AAV patients compared to control subjects. CIMT is considered an early atherosclerosis marker which is associated with cardiovascular risk [4,11]. Thus, increased CIMT may explain the increased incidence of CV disease in this patient group. Hatri et al., measured CIMT in 64 Takayasu arteritis patients and they showed that CIMT was significantly higher than the control group [12]. Another study including 103 systemic lupus erythematosus (SLE) patients and 30 healthy controls demonstrated that increased CIMT was more frequent in patients with SLE [13]. Increased age and inflammation both play a central role in accelerated atherosclerosis, which in turn may be responsible for increased cardiovascular mortality.

Arterial stiffness is an independent predictor of cardiovascular risk. Therefore, measuring arterial stiffness using PWV and AI may provide further information in addition to traditional risk factors [14,15]. Booth at al., reported that arterial stiffness was higher in patients with active AAV than healthy controls by measuring PWV and pulse waveforms [9]. Moreover, they also demonstrated that arterial stiffness was positively correlated with CRP but not with disease duration, ANCA status or the total dose of steroids. Arterial stiffness in patients with remission was similar to controls. Therefore, arterial stiffness appears to be associated with active inflammation. In our study we also found that arterial stiffness was similar in patients in remission and healthy controls.

In the present study, correlation analysis showed that CIMT was positively correlated with age and PWV. A recent review demonstrated that there was a linear relation between CIMT and age in healthy population, suggesting that CIMT progresses linearly with older age [16]. Similar findings between CIMT and age are also supported with several studies [17,18]. Although, PWV was similar between the two groups, it was correlated with CIMT which shows early atherosclerosis. The lack of a difference between AAV patients and controls regarding PWV values was probably due to the fact that the vast majority of our patients were in remission. The positive correlation between CIMT and PWV supports the notion that PWV is indeed an indicator of cardiovascular risk. Also, it is well defined in the literature that increased arterial stiffness is associated with accelerated atherosclerosis in patients with primary systemic vasculitis patients [19,20].

Previous studies have shown classic cardiovascular risk factors such as hypertension and dyslipidemia to be more common in AAV [21,22]. Non-traditional risk factors such as chronic

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vascular inflammation may also lead to endothelial dysfunction resulting in accelerated atherosclerosis in these patients [23]. In our study, although, most of the patients were in remission, CRP levels were still significantly higher than controls. However, we did not find an association between CRP, CIMT or arterial stiffness. This could be due to the low patient number or the fact that the majority of our patients were in remission. However, CRP is a risk factor for atherosclerosis and may very well be another link between inflammation and accelerated atherosclerosis in vasculitis [24].

The association between steroids and CIMT measurements reveal conflicting results in patients with AAV. While some data suggest that steroids may accelerate atherogenesis in AAV patients, other studies do not support this finding [25]. There is no data in the literature regarding the relationship between immunosuppressives other than steroids and CIMT in AAV patients. Some studies suggest that rituximab may decrease CIMT in rheumatoid arthritis patients [26]. According to another study involving 82 lupus nephritis patients, there were no associations between CIMT and the cumulative dose or duration of steroids, hydroxychloroquine, azathioprine, mycophenolic acid and cyclophosphamide [27].

The major study limitations were cross-sectional design and small sample size. There was no prospective follow-up of cardiovascular events. Immunosuppressive use including steroids was another confounding factor. Lastly, we were unable to evaluate the effect of active disease on aortic stiffness, CIMT or other traditional parameters since the majority of our AAV patients were in remission.

Conclusion

The present study showed that CIMT is significantly increased and correlated with age and PWV in patients with AAV compared to controls. CIMT can be used as a screening tool as part of patient follow-up to identify patients at cardiac risk.

Compliance with Ethical Standards

Ethical approval: The study was approved by the Marmara University, School of Medicine, Clinical Research Ethics Committee (date/no: 2018/09.2018.653).

All participants gave written informed consent.

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Conflict of interest : The authors declare that there is no conflict of interest.

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