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Original Article

High Resolution B-Mode Ultrasonography in Evaluation of Atherosclerosis in Patients with Rheumatoid Arthritis

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Abstract:

Rheumatoid arthritis is a chronic, systemic, autoimmune inflammatory disorder affecting various tissues and organs like skin, blood vessels, heart, lungs, and muscles. Vasculitis is an important one of the extra-articular manifestations, leading to gradual thickening of intima-media and atherosclerotic arterial disease. This case control study was carried out to compare the intima-media thickening of both the common carotid and femoral artery between rheumatoid and non-rheumatoid arthritis subjects by high resolution B-mode ultrasonography as well as assessing plaque prevalence in the common carotid artery in Rheumatoid arthritis and morphologic evidence of sub-clinical atherosclerosis in RA patients. Total 40 adult patients with rheumatoid arthritis were taken as cases & 20 matched healthy people were taken as controls. Common Carotid artery intima-media thickness was greater in patients than in controls (mean ± SD 0.52 ±0.09 vs 0.37± 0.08mm, p<0.001). Similarly, the intima medias of both right and left femoral arteries of the Rheumatoid arthritis patients were considerably thicker than controls (0.67 ± 0.19 vs. 0.39±0.04, p< 0.001 and 0.62±0.17 vs.0.39 ±0.04, p<0.001). Six cases (15%) had calcification at femoral arteries. None of the controls exhibited plaque or calcification in any parts of common carotid or femoral arteries. The outcomes of the present study specified that Rheumatoid arthritis patients had increased thickness of intima media of the carotid and femoral artery which were the manifestations of atherosclerosis. Rheumatoid arthritis was usually associated with increased arterial wall thickness with or without plaque or calcification.

Key words: B-Mode Ultrasonography, Atherosclerosis, Rheumatoid arthritis.

Introduction:

Patients with rheumatoid arthritis (RA) have an increased morbidity and mortality due to cardiovascular disease (CVD). Traditional cardio-vascular risk factors can't fully explain the increase but inflammation has been shown to contribute to the increased CVD among these patients[1,2]. Some studies have previously demonstrated that patients with RA have pre-mature atherosclerosis as measured by increased intima-media thickness (IMT) of the common carotid artery (CCA)

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compared with controls[3]. B- mode ultrasonography of the carotid artery is nowadays increasingly being used as a non-invasive and well-validated tool for assessment of atherosclerotic burden in a variety of clinical conditions[4]. Atherosclerotic changes in the carotid artery (e.g., thickened intima-media complex, presence of plaque, rough arterial wall, calcifications) and other structural abnormalities detected by high-resolution ultrasound are strongly associated with several classic cardio-vascular risk factors[5]. A prime example of this association is an increased prevalence of carotid plaques in patients with familial hypercholesterolemia and arterial hypertension, warranting further investigations to assess the level of the carotid artery stenosis and titrating of lipid-lowering agents, anti-hypertensive therapy and or invasive surgical procedures[6]. Increased IMT, measured by ultrasound is regarded to be an early indicator of overall atherosclerosis and several studies on IMT in the general population have shown a relationship between increased IMT and future CV event[7]. Among patients with RA, increased IMT has been associated with traditional CV risk factors, including age & sex, markers of inflammation, and disease duration[3]. The carotid arteries are easily accessible to ultrasound techniques and these techniques provide accurate and reliable measurement of atherosclerosis in the sub-clinical stages[8]. These techniques have been widely used in large population-based epidemiologic studies, evaluating the prevalence and risk factors of atherosclerosis, as well as in high-risk populations, including patients with non-insulin-dependent diabetes mellitus (NIDDM)[9], familial hypercholesterolemia[10], hypertension[11] and systemic lupus erythematosus (SLE)[12]. Thus, if RA increases the risk of atherosclerosis as in these disorders, one can logically hypothesize, that those RA patients would have sub-clinical morphologic evidence detectable by these techniques. Aim of this study was to compare the IMT of both the CCA and FA between rheumatoid and non-rheumatoid arthritis subjects by B-mode USG.

Materials and Methods:

This case control study was carried out in the Department of Radiology & Imaging, Bangabandhu Sheikh Mujib Medical University (BSMMU), in collaboration with the Departments of Medicine, Rheumatology and Physical Medicine of the same hospital "between" July 2020 to March 2021. A total of 60 patients were recruited. Of them 40 were Rheumatoid arthritis (RA) patients (cases) and 20 were healthy adults (controls). Patients of RA and healthy control without any evidence of atherosclerosis who attended in the above-mentioned places were the study population. Keeping compliance with Helsinki Declaration for Medical Research Involving Human Subjects 1964, the study subjects were informed about the study design, the purpose of the study and their right for withdrawing themselves from the project at any time, for any reason. Patients who voluntarily gave informed written consent to participate in the study were included as the study sample. Ethical clearance was taken from the hospital. Clinical variables reflecting RA disease activity were measured, including the patient's global assessment, physician's global assessment, physical disability score, acute-phase reactant levels, patient's assessment of pain, number of tender, swollen, and deformed joints, and duration of morning stiffness. Data were also collected on the RA test and radiographic status of involved joints in the hands and wrists. To avoid confounding effects by other known risk factors for atherosclerosis, we used the following exclusion criteria: hypertension, as defined by blood pressure >150/90 mm Hg or use of antihypertensive medication; hyperlipidemia, as defined by levels of total cholesterol>250 mg/dl, low-density lipoprotein (LDL) cholesterol >160 mg/dl, or triglycerides >200 mg/dl, or the use of lipid-lowering medication; diabetes mellitus, as diagnosed according to the World Health Organization criteria or use of anti-diabetic medication; and history of ischemic heart disease or cerebrovascular events. Inclusion criteria for cases were patients who fulfilled the 1987 American Rheumatism Association criteria for RA, and were diagnosed by a consultant rheumatologist. Every patient had disease duration of at least 5 yrs. Inclusion criteria for controls were adult healthy subjects who gave informed consent for their inclusion in the study but no history of inflammatory arthritis or vascular disease. Patients having connective tissue diseases other than RA, having associated comorbidities like HTN, DM, Dyslipidemia, patients on antihypertensive, anti-diabetic, antidyslipidemic or corticosteroid drugs were excluded from the study. High resolution B-Mode ultrasonography was done at Radiology and Imaging Department of BSMMU, Dhaka. Data were processed and analyzed using SPSS (Statistical Package for Social Science). The statistical tests used to analyze the data were student's t-test and Chi-squared (X^2) test. The level of significance was set at 0.05 and < 0.05 considered significant.

Results:

Majority of the patients in the both case (90%) and control (88.9%) groups was non-smoker. Rheumatoid arthritis (RA) test was positive in 34(85%) of 40 Rheumatoid arthritis patients.

Baseline disease activity in cases shows that the mean swollen joint count and tender joint count were 3 (range: 1-5) & 4 (range:1-5) respectively. The mean duration of morning stiffness was 104.2+37.5 minutes. The mean pain score was 7.1±1.2cm on visual analogue scale (VAS) (Table I).

Table I: Disease activity in case group at baseline (n=40).

Disease activity in cases at baseline	Mean ± SD	Range
Swollen joint count	3±1	1-5
Tender joint count	3±1	1-5
Duration of morning stiffness (min)	104.2±37.5	60-180
Pain VAS (0-10cm)	7.1±1.2	5-9
Patients' global VAS (0-10cm)	7.3±1.1	5-9

The mean systolic & diastolic blood pressures of the cases were 1l6 mm of Hg (range: 95-140 mm of Hg) and 76 mm of Hg (range: 65-110 mm of Hg). The average erythrocyte sedimentation rate (ESR), total platelet count, total WBC count & c-reactive protein (CRP) were 51.3±4.9 mm at the end of 1 hour (range: 10-125 mm), 286.4x109±4.9/ L (range: $70x10^9$-$500x10^9$), 47.9±25.3/ml (range: 7.26-450/m1) and 11±1.7mg/L (range: 5.84-8.4mg/L) respectively (Table II).

Table II: Distribution of cases by physical examination & laboratory findings (n=40).

Disease activity in cases at baseline	Mean ±SD	Range
Systolic BP (mm Hg)	116±15	95-140
Diastolic BP (mmHg)	76±9	65-110
ESR (mm)	51.3±4.9	10-125
Total platelet count	286.4×109±4.9	$70×10^9$- $500×10^9$
Total WBC count	47.9±25.3	7.26-450
C-reactive protein (mg/L)	11±1.7	5.84-8.4

The intima medias of both right & left common carotid arteries of case group were significantly thicker than those of the control group (0.52±0.09 vs. 0.37+0.08, p<0.001 and 0.58±0.13 vs. 0.38±0.09, p<0.001) (Table III).

Table III: Intima media thickness of common carotid artery.

	Group		
Intima media thickness (mm)	Case (n=40)	Control (n=20)	P value
Right common carotid artery	0.52 ± 0.09	0.37 ± 0.08	<0.001
Left common carotid artery	0.58 ± 0.13	0.38 ± 0.09	<0.001

* Data were analyzed using Student's t-Test and presented as Mean ± SD

The intima medias of both right & left femoral arteries of the former group were considerably thicker than those of the control group (0.67±0.19 vs. 0.39±0.04, p<0.001 and 0.62±0.17 vs. 0.39±0.04, p<0.001) (Table IV).

Table IV: Intima media thickness of common carotid artery.

	Group		
Intima media thickness (mm)	Case (n—40)	Control (n=20)	P value
Right femoral artery	0.67 ± 0.19	0.39 ± 0.04	<0.001
Left femoral artery	0.62 ± 0.17	0.39 ± 0.04	<0.001

* Data were analyzed using Student's t-Test and presented as Mean ± SD

Two patients (5%) in case group had plaque and the mean plaque size was 2.7±0.1 mm, while 6 of the cases had calcification. Of the 6 cases, 4 were in the right femoral artery and 2 were in the left femoral artery (Table V).

Table V: Distribution of the study population based on plaque & calcification.

Outcomes	Case (n=40)	Control (n=20)
Plaque	2 (5%)	0
Plaque size (mm)	2.7±0.1	0
Calcification	6 (15%)	0
Site of calcification		
Right FA	4 (66.7%)	0
Left FA	2 (33.3%)	0

Discussion:

The present study was aimed to found evidence of subclinical atherosclerosis (in terms of intima-media thickness) by carotid ultrasound in patients presenting with RA using the technique of B-mode ultrasound. The study observed that intima-media of both the right & left common carotid arteries of the case group were significantly thicker than those of the control group ($p<0.001$). Similarly, the intima-media of both the right and left femoral arteries were considerably thicker than those of the control group ($p<0.001$). Two (5%) of 40 patients in the case group exhibited plaque and the mean plaque size was 2.7 mm, while had calcification. Of them, 4 (66.7%) had calcification in the right femoral artery (right FA) and 2 (33.3%) in the left FA.

Hannawi S et al. were the first to show an increased carotid IMT and increased plaque indicating accelerated atherosclerosis in patients at first presentation with symptoms of RA which are consistent with the findings of our study[13].

Manzi et al used an accurate and reliable imaging technique, high-resolution B-mode ultrasound, for the diagnosis of sub-clinical atherosclerosis and demonstrated that RA patients had greater IMT of the CCA than did appropriately matched controls[12].

Regarding carotid plaque, several studies reported no difference in plaque prevalence and plaque size, whereas others have found increased carotid plaque in RA patients[14].

Kumeda Y et a1. added that IMTs of the common carotid arteries were significantly higher in the 138 RA patients (0.641+ 0.l27 mm) than in the 94 control subjects (0.576 + 0. ll5 mm) ($p <0.001$). The femoral artery IMT was also significantly higher in the RA patient group (0.632±0.125 mm) than in the control group (0.593 ± 0.141mm) ($p=0.0124$)[15]. Abu-Shakra M et al. in his study shown that the carotid artery IMT or carotid plaque are maker of atherosclerotic burden and correlates with cerebrovascular outcome[16]. Alkaabi JK et al. found that the patients with established RA have been shown to exhibit significantly greater carotid IMT or plaque than matched control subjects[17].

Favoring the findings of the present study, previous studies identified inflammatory activity to be important for the development of CV disease in RA, even after adjustment for traditional CV risk factors. The consistent association of carotid IMT with inflammatory markers supports the evidence that CV mortality in RA patients is associated with inflammation. Previous studies have consistently shown that excess CV mortality in RA is associated with baseline or subsequent evidence of high levels of inflammation, including elevated CRP, elevated erythrocyte sedimentation rate, and elevated swollen joint counts.

Several studies also demonstrate the association of older age at RA onset, smoking, hypertension, and male gender on CV mortality[18,19]. In the present study, RA patients were older and significantly overweight or obese than their healthy counterparts. The carotid IMT assesses the atherosclerotic burden and provides information that is independent and incremental to that provided by standard risk factors. Non-invasive tools such as ultrasound measurement of the carotid IMT may be useful to better understand risk levels in primary prevention.

The data therefore strongly suggest that the pathogenesis of atherosclerosis is linked to that of auto-immune joint disease which is consistent with previous studies demonstrating either early CV mortality after onset of inflammatory polyarthritis or increased risk of CV death already present at RA diagnosis.

Conclusion:

The study concludes that RA patients generally have increased thickness of intima-media of the carotid & femoral arteries which are the early manifestations of atherosclerosis. The result suggests that RA itself may lead to increased arterial wall thickening, possibly due to an increase in the inflammatory process (vasculitis). Therefore, RA patients should undergo routine screening for cardiovascular risk factors, including hypertension, hyperlipidemia, and diabetes, to identify those at high risk for atherosclerosis. Aggressive management of traditional cardiovascular risk factors in RA patients should be implemented, including lifestyle modifications, pharmacologic interventions, and appropriate monitoring to prevent and treat atherosclerosis. Further research is needed to develop more effective therapies for preventing and treating atherosclerosis in RA patients, including targeting the inflammatory pathways involved in both RA and atherosclerosis. Collaboration between rheumatologists and cardiologists is crucial to ensure that RA patients

receive optimal care for their joint disease and their associated cardiovascular risks. Education and awareness campaigns should be developed to increase understanding among healthcare providers and patients about the increased risk of atherosclerosis in RA patients and the importance of early detection and management of cardiovascular risk factors.

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