Original Article

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Comparison of Carotid Ultrasound Parameters in Patients with Rheumatoid Arthritis and Control Subjects: A Cross-sectional Study

Radiology Section

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ABSTRACT

Introduction: Rheumatoid Arthritis (RA) is considered one of the risk factors for Cardiovascular Disease (CVD). Carotid ultrasound is used to assess the extent of subclinical atherosclerosis in patients with RA. Very few studies have evaluated all carotid ultrasound findings, such as Carotid Intima-media Thickness (CIMT), carotid diameters like Luminal Diameter (LD) and Interadventitial Diameter (IAD), and plaque characteristics in patients with RA.

Aim: To assess and compare the various carotid parameters in RA patients with controls and also to evaluate their association with age and duration of onset of the disease.

Materials and Methods: A single-centre cross-sectional study was conducted at the Department of Radiology, GCS Medical College and Hospital, Ahmedabad, Gujarat, India, involving 40 patients with RA (Group-RA) and 40 controls (Group-C). Patients were further divided into three age subgroups. Carotid ultrasound parameters like CIMT, LD, IAD, and plaque were evaluated in both groups. Continuous variables were analysed using the t-test, and categorical data were analysed using the Chi-squared test. A p-value of <0.05 was considered statistically significant.

Results: Age- and sex-matched controls were included with 28 females and 12 males in both the study groups. The mean LD and IAD were significantly higher in the RA group than in controls (Mean LD- 5.88±0.97 mm vs 5.26±1.08 mm with p=0.009; Mean IAD- 6.85±0.89 mm vs 6.30±0.87 mm with p=0.006). The mean CIMT was higher in the RA group but not statistically significant (0.57±0.13 mm vs 0.54±0.12 mm with p=0.256). Further subgroup analysis showed that all carotid parameters were statistically significant in the 31-60 years age group as compared to 18-30 years and 61-80 years subgroups. The effect of the duration of the disease (>5 years) on the carotid parameters was also significantly higher in the 30-60 age group (p<0.001).

Conclusion: The present study showed that various carotid ultrasound parameters can be used as a screening tool in the follow-up of RA patients to detect early changes in atherosclerosis, with LD and IAD having superior predictive capability. The study further showed that carotid ultrasound parameters have a better predictive value in the 31-60 years age group.

Keywords: Atherosclerosis, Carotid intima media thickness, Interadventitial diameter, Lumen diameter

INTRODUCTION

The RA is the most common autoimmune arthritis with a prevalence of up to 1% [1]. It is considered one of the risk factors for CVD, and the chronic inflammatory process is the underlying cause of atherosclerosis [2]. To assess the extent of subclinical atherosclerosis and the burden of CVD in RA, many non-invasive screening techniques are being used. One of these non-invasive screening techniques is carotid ultrasound, in which we measure the CIMT [3,4].

The CIMT and plaque measurements on carotid ultrasound have been assessed as early indicators of systemic atherosclerosis in non-RA populations [5-7]. CIMT and carotid plaque characteristics could also potentially prognosticate CV events in patients [8], but few studies showed discrete results [9-11]. Although CIMT and plaque are commonly used parameters to assess atherosclerosis, carotid diameters such as LD and IAD are also key indicators of arterial remodelling and can be used to assess atherosclerotic changes [12,13].

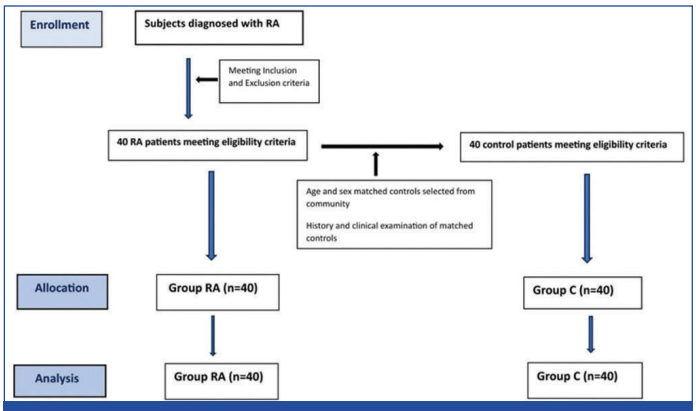
So far, only a single study has included carotid diameters (LD, IAD) with IMT in carotid ultrasound in patients with RA, but it was restricted to the female population [14]. Our study aimed to assess and compare the CIMT, plaque, and carotid diameters in RA patients with controls of both genders and also to evaluate the association of carotid ultrasound features with age and duration of onset of the disease.

MATERIALS AND METHODS

This was a single-centre cross-sectional study involving a total of 80 subjects, with 40 in each group (Group RA and Group Controls), conducted in the Department of Radiology, GCS Medical College and Hospital, Ahmedabad, Gujarat, India, from June 2021 to May 2022.

Sample size calculation: The sample size for the present study was calculated based on the study done by Mohan A et al., which showed the prevalence of asymptomatic atherosclerosis in RA patients as 50%, assumed to be four times that observed in the general population [15], with α=5% and a study power of 80% (1-β). The sample size was calculated to be 32 in each group; hence, we included 40 patients in each group. The flowchart is depicted in [Table/Fig-1].

Inclusion and Exclusion criteria: The inclusion criteria encompassed adults aged 18 to 80 years diagnosed with RA who met the American



[Table/Fig-1]: Flowchart of recruitment of subjects.

College of Rheumatology criteria for RA for a minimum of two years. Patients willing to undergo carotid doppler using B-mode ultrasound to measure CIMT were included. Patients with disease younger than 16 years of age and those with RA overlapping with other rheumatic diseases were excluded. Additionally, patients with a history of type II diabetes mellitus, hypertension, cerebrovascular disease, peripheral vascular disease, coronary artery disease, chronic liver failure, hypothyroidism, and chronic renal failure were excluded. Patients who were pregnant or had a history of pregnancy within the last three months were also excluded.

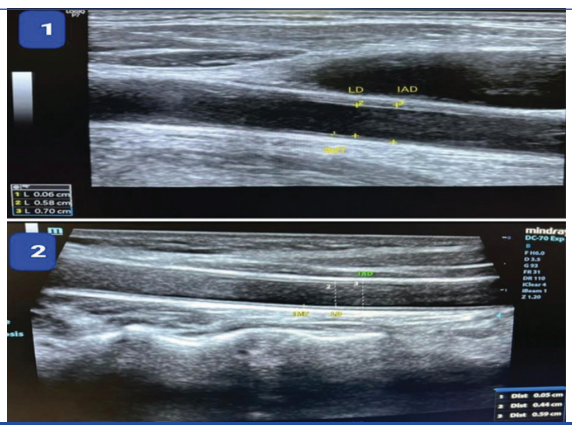
Study Procedure

Control subjects without RA were selected from the community and recruited based on socio-demographic matching characteristics such as age, sex, co-morbidities, and the absence of atherosclerotic CVD. All patients underwent a clinical evaluation, including socio-demographic, personal, medical, and treatment history, along with a physical examination.

Patients meeting the inclusion criteria were informed about the study's nature and registered after obtaining written informed consent. Subjects were further divided into three subgroups based on their age (18-30 years, 31-60 years, 61-80 years). RA patients were further classified according to the duration of disease onset (<5 years and >5 years). Carotid ultrasound parameters were obtained for all subjects.

Carotid ultrasound measurements: Carotid and vertebral artery ultrasound were performed using a GE Logiq P5 color Doppler machine with a high-frequency linear transducer (4-10 MHz) and a Mindray Ultrasonography (USG) machine with a high-frequency linear transducer (8-10 MHz).

The carotid ultrasound was performed in a supine position, with the left and right arteries scanned in transverse and longitudinal planes at end-diastole. Greyscale, spectral, and colour Doppler ultrasonography were conducted for the near and far walls of the carotid bulb 2 cm below its bifurcation, as well as the internal and external carotid arteries bilaterally. The intima-lumen interface, IMT, and media-adventitia interface were calculated, with the average of both arteries considered. The LD was measured as the distance from the near wall to the far wall of the lumen-intima interface. The intra-adventitial diameter was determined by measuring the distance between the adventitia-media interfaces. Measurements of carotid ultrasound parameters assessed in control and RA patients are shown in [Table/Fig-2].



[Table/Fig-2]: Ultrasound image a) Shows carotid ultrasound in RA patient; and b) Shows carotid ultrasound in control subject. Increased carotid ultrasound parameters are noted in RA patient as compared to control.

Velocities were calculated at a Doppler angle of 45° to 60°. An intimal-medial thickness ≥0.9 mm was considered elevated [16]. A CIMT ≥1.2 mm or a focal narrowing ≥0.5 mm of the surrounding lumen was taken as the measurement for Carotid plaque [16]. An experienced sonographer performed the ultrasound without prior knowledge of the clinical and angiographic parameters of the patients. Carotid ultrasound was conducted in both cases and controls.

STATISTICAL ANALYSIS

Continuous distributed variables were presented as mean {Standard Deviation (SD)} and median {Interquartile Range (IQR)}, and groups were compared using the Student's t-test. Categorical data were analysed and compared using the Chi-squared test. All statistical analyses were performed using Statistical Package for Social Sciences (SPSS) 22.0 software. A p-value of <0.05 was considered statistically significant.

RESULTS

Among a total of 80 participants there were 28 females and 12 males each in both study groups [Table/Fig-3].

Variables	Group-R	Group-C	p-value
Sex			
Female	28	28	1
Male	12	12	1
Age (years)			
18-30	8	8	1
31-60	23	23	1
61-80	9	9	1
Smokers	8	10	0.594
Disease duration in Group-RA			
≥5 years	17	0	-
<5 years	23	0	-

[Table/Fig-3]: Demographic data between two groups.
Chi-squared test

Mean CIMT, LD, and IAD were found to be higher in the RA group compared to the control group. However, only LD and IAD showed statistically significant values [Table/Fig-4].

Variables	Group-RA	Group-C	p-value
CIMT (in mm)	0.5770±0.13	0.5425±.12	0.256
LD (in mm)	5.8825±.97	5.2650±1.08	**0.009**
IAD (in mm)	6.85±0.89	6.30±.87	**0.006**

[Table/Fig-4]: Carotid ultrasound parameters in the RA and control groups (expressed as Mean±SD).
Student's t-test

The mean age was comparable between the two study group with P=0.91. (Mean ± SD of Group RA was 45.07±14.29, and that of Group C was 45.4± 13.63). The RA group and the controls were divided into three age subgroups. The first age subgroup was 18-30 years (n=8), the second was 31-60 years (n=23), and the third was 61-80 years (n=9). It was observed that in the three age subgroups, carotid parameters were higher in the RA group compared to the control group. However, statistically significant values were observed only in the 31-60 age subgroup for all the carotid parameters (31-60 year age subgroup- mean CIMT showed a p-value of 0.042; mean LD had a p-value of <0.001; mean IAD had a p-value of <0.001) [Table/Fig-5].

In the RA study group, patients were again divided according to the duration of the disease. A total of 17 subjects had a disease duration of <5 years, and 23 subjects had a disease duration of >5 years. The mean CIMT was 0.60+0.07 mm vs 0.55+0.05 mm; mean LD was 6.1+0.43 mm vs 5.7+0.33 mm, and the mean IAD 6.8+0.50 mm vs 6.5+0.45 mm. All three parameters were significantly higher in RA patients with >5 years duration (p<0.05). It was observed that all three carotid parameters were higher in all age subgroups with a duration of disease >5 years. However, statistically significant values were observed in the 31-60 years age subgroup. (all three carotid ultrasound parameters showed p<0.001) [Table/Fig-6].

Variables	Group-RA	Group-C	p-value
CIMT (18-30 y)	0.40±0.08	0.38±0.06	0.209
CIMT (31-60 y)	0.55±0.06	0.52±0.07	0.042
CIMT (61-80 y)	0.77±0.06	0.74±0.09	0.083
LD (18-30 y)	4.68±0.31	4.53±0.39	0.06
LD (31-60 y)	5.7±0.49	4.87±0.54	<0.001
LD (61-80 y)	7.33±0.38	7.17±0.4	0.07
IAD (18-30 y)	5.45±0.23	5.34±0.28	0.058
IAD (31-60 y)	6.89±0.35	6.11±0.49	<0.001
IAD (61-80 y)	7.82±0.12	7.76±0.17	0.07

[Table/Fig-5]: Carotid ultrasound parameters of RA and controls in each age subgroups.
Student's t-test

Variables	<5 years duration (n=17)	≥5 years duration (n=23)	p-value
CIMT (18-30 y)	0.40±0.06	0.42±0.04	0.083
CIMT (31-60 y)	0.50±0.02	0.58±0.06	<0.001
CIMT (61-80 y)	0.76±0.08	0.78±0.03	0.142
LD (18-30 y)	4.79± 0.27	4.93±0.38	0.06
LD (31-60 y)	5.25±0.26	5.89±0.44	<0.001
LD (61-80 y)	7.25±0.33	7.38±0.44	0.1390
IAD (18-30 y)	5.45±0.15	5.54±0.26	0.06
IAD (31-60 y)	6.47±0.18	7.08±0.22	<0.001
IAD (61-80 y)	7.86±0.13	7.93±0.26	0.1318

[Table/Fig-6]: Carotid ultrasound parameters in each age subgroup of RA subjects in relation to duration of disease.
Student's t-test

Plaque formation was observed in both RA patients and controls. Bilateral plaques were found in seven patients in the RA group (17.5%) and three members in the control group (7.5%) (p-value-0.179). A total of 17 patients in the RA group (42.5%) and 9 members in the control group (22.5%) had unilateral carotid plaques (p-value=0.057).

The plaque morphology was homogenous in 13 patients in the RA group (54.1%) and 6 members in the control group (50%), while heterogeneous plaques were in 9 (37.5%) and 3 members (25%) in the RA and control groups, respectively (p-value=0.061). Two plaques from patients in the RA group and three plaques in the control group were calcified. The present study showed that bilateral carotid plaques were found more than twice in RA than in controls (17.5% vs 7.5%). In plaque morphology, heterogeneous plaques were also more common in RA patients than controls (37.5% vs 25%).

DISCUSSION

In the present study, CIMT and carotid diameters were found to increase linearly with age in both study and control subjects. Similar results were obtained by Van den Munckhof ICL et al., and Tosetto A et al., [17,18]. There is evidence of an increase in atherosclerosis with age. Hence, the carotid parameters that indicate subclinical atherosclerosis will also increase linearly with age.

The mean CIMT was not significantly higher in RA patients than in controls. However, the other diameters (mean LD and IAD) showed statistical differences between RA patients and controls. Similar results were obtained by Schott LL et al., [14]. This can be explained by the fact that inflammatory and protease activities in RA cause arterial remodelling in the early stages. During the process of early vascular remodelling, a concomitant increase in carotid diameters can occur (i.e., outward radial enlargement), while allowing the lumen cross-sectional area and IMT/plaque to be maintained constant by distributing them over a larger area [12]. However, in a later stage of vascular remodelling, the continued formation of plaque/IMT can ultimately cause a reduction in blood flow. This shows that enlarged diameters can be considered a sign of vascular adaptation and a marker of early atherosclerosis than CIMT [14]. The RA patients scanned in the present study may have had the early changes of vascular remodelling in the arteries.

In the RA study group, there was a significant increase in mean CIMT, LD, and IADs with increased disease duration (>5 years). Similar results were observed in the study by Mahajan V et al., who obtained that the mean CIMT in RA patients (>3 years) was (0.595±0.18 mm) vs (0.519±0.32 mm) in RA patients (<3 years), and CIMT was significantly greater with increased disease duration [19]. Similar results were also seen in the study by Shravan Kumar P et al., [20]. The mean value of CIMT in Group-I (1±047 years) was 0.703±0.09 mm; in Group-II (3.35±0.65 years) was 0.791±0.146 mm, and in Group-III (11.6±3.68 years) was 0.91±0.136 mm. The increase in CIMT with duration was significant. It may be attributed to the fact that more years of exposure lead to increased inflammation and other factors such as increased arterial stiffness and prothrombotic markers in patients with RA [21]. The role of inflammation as a basic pathogenic mechanism in atherosclerosis is also well known. Hence, increased disease duration leads to increased atherosclerotic changes.

In the 18-30 and 61-80-year subgroups, CIMT, LD, and IAD were not significantly higher in patients with RA compared with controls. Similarly, the effect of increased duration of disease (>5 years) on the carotid parameters in RA patients was also not significant in the 18-30 years and 61-80 years subgroups. The plausible explanation for these findings could be that in the study in the 18- to 30-year age subgroup, the number of patients with >5 years of duration was lower. Hence, the effect of the increased disease duration/increased inflammation on the carotid parameters was seen less significantly in RA patients compared to controls. Whereas, in the elderly age group (61-80 years), age-related atherosclerotic changes also occur, confounding the effect of inflammation as a risk factor for atherosclerosis. Therefore, in the present study, the 31-60-year-old subgroup showed a significant increase in carotid parameters in RA patients. This was similar to the results of the study by Gauri LA et al., who obtained similar results in <50 years of age (mean CIMT in RA patients was (0.5996±0.109 mm) vs (0.5290±0.006 mm) in the control group) [22].

Bilateral carotid plaques were found more than twice as often in RA than in controls. In plaque morphology, heterogeneous plaques were more common in RA patients. Similar results were observed in the study by Wah-Suarez MI et al., [23]. The findings can be attributed to the fact that the chronic inflammatory process in RA can amplify the process of atherosclerosis [24]. The systemic inflammation in RA releases proinflammatory cytokines which contribute to endothelial dysfunction, leading to the earlier and faster progression of atherosclerotic plaques.

As far as authors know, the present research was the first attempt to incorporate measurements of carotid diameter in conjunction with other parameters assessed through carotid ultrasound in assessing atherosclerotic risk in patients with RA, spanning both genders.

Limitation(s)

The limitations of the present study were that the sample size was small and was obtained from a single region of ethnicity. Therefore, further studies regarding the effect of disease duration can be carried out with a larger sample size extending to multiple ethnic groups. To avoid the effect of other confounding factors on carotid ultrasound parameters, the authors chose patients without co-morbidities and complications of RA. Therefore, further studies involving patients with such aspects can be carried out on a larger scale. Additional research involving extensive, multicentre trials that encompass RA patients with co-morbidities can be conducted to evaluate the impact of complications or anti-rheumatoid drug treatments on carotid diameters or parameters.

CONCLUSION(S)

The present research demonstrated that carotid ultrasound parameters have the potential to function as a screening tool for monitoring RA patients and detecting early changes of atherosclerosis. Among these parameters, LD and IAD were found to exhibit superior predictive capabilities. Moreover, the study found that carotid ultrasound parameters possess a more favourable predictive value in individuals aged 31-60 years.

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