Endothelial dysfunction and subclinical atherosclerosis as evidenced by the measurement of flow mediated dilatation of brachial artery and carotid intima media thickness in patients with rheumatoid arthritis

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Abstract  Aim of the work: The present study aimed at evaluating the prevalence of subclinical atherosclerosis and cardiovascular disease by means of assessment of carotid intima media thickness and endothelium dependent function through assessment of brachial artery flow mediated dilatation in patients with rheumatoid arthritis. Materials and methods: Twenty six patients with rheumatoid arthritis and 20 healthy control subjects underwent measurement of brachial artery FMD and CIMT using B-mode gray scale US for evaluating cardiovascular risk. Results: The brachial artery FMD was –96.6–6.6% in rheumatoid arthritis (indicating ED), and 20–25% in the control group. The CIMT was 0.50–0.72 mm in rheumatoid arthritis and 0.35–0.47 mm in the control group. Conclusion: The results from the present study support the use of carotid US and endothelial function assessment by means of FMD as a useful tool to predict the increased risk of cardiovascular...
1. Introduction

Rheumatoid arthritis (RA) is the most common systemic autoimmune disease. Patients with rheumatoid arthritis are at increased risk for cardiovascular diseases (CVD), one of the earliest manifestations of CVD is endothelial dysfunction (ED) (1). The endothelium is the innermost lining of the vasculature and is responsible for maintaining vascular homeostasis via the balanced production of a number of vasoactive factors such as nitric oxide (NO) which play an important role in vasodilatation and inhibiting the atherosclerotic process (2). Damage to the endothelium can reduce (NO) activity, causing endothelial dysfunction which is an early indicator of CVD (3). ED is an important sign of early atherosclerosis and can be assessed non-invasively by the impairment of endothelial dependant flow mediated vasodilatation (ED-FMD) of peripheral arteries measured by US (4). Increased carotid intima–media thickness (CIMT), measured by US, is also regarded as an early indicator of atherosclerosis and future CVD (5).

2. Patients and methods

2.1. Patients and control

The subjects in the present study were 26 RA patients (23 females and 3 males), and 20 healthy control subjects. All patients have the following criteria: ages between 35 and 60 years, non tobacco users, did not present other autoimmune diseases, hypertension, diabetes mellitus, dyslipidemia, renal insufficiency or received drugs affecting the cardiovascular system.

20 healthy volunteers were recruited as control. Written consent was taken from all patients and the control group and the institutional ethics committee approved the study protocol.

2.2. Methods: Radiological assessment by US

2.2.1. Carotid US

The subject was made to lie supine with slight hyperextension of the neck. Both common carotid arteries were examined using a 7 MHz linear array transducer in a PHILIPS HD11 instrument. Carotid intima–media thickness and lumen diameter were measured from end diastolic M-mode images (minimum distension) of the wall of the distal common carotid artery in a location not containing plaque. The greater distance between lumen–intima and media-adventitia interface was measured. The mean value of the two sides was taken.

2.3. Flow mediated vasodilatation of brachial artery

The procedure was performed on the same US machine and the same transducer as used in carotid US.

The subject lies in a supine position; the right brachial artery was scanned in longitudinal section 2–15 cm. above the antecubital fossa with B-mode. The clearest picture of the artery at the center was obtained (the transducer was kept constant throughout the procedure by noting the relation of the artery with the adjacent anatomical landmarks). The luminal diameter of the artery was measured by calculating the distance between the proximal and distal intima. Ischemia was induced with a sphygmomanometer cuff placed around the forearm distal to the scanned region inflated to 200 mmHG for 4 min and then released. A second scan was taken at this stage and the luminal diameter was measured 60 s. after cuff deflation. The endothelium dependant function is defined by the formula: D2/D1x100. The higher the numeric value of the study, the better the endothelial function. ED is considered when the FMD is < 4.55.

<table>
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<tr>
<th>Number</th>
<th>D1 (mm)</th>
<th>D2 (mm)</th>
<th>FMD (%)</th>
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<tr>
<td>5</td>
<td>2.5</td>
<td>3</td>
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<td>7</td>
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<td>3.7</td>
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3. Results

This study included 26 patients of rheumatoid arthritis with an age range of 35–60 years and 20 healthy control subjects with the same age range.

Table 1 shows the characteristics of the study group in which the diameter of the brachial artery before the induction of ischemia (D1) was 2.5 mm in five subjects, after the release of ischemia (D2) 3 mm, the FMD was 20%. D1 was 3 mm in seven subjects, D2 was 3.7 mm and FMD was 23.3%. D1 was 3.2 in eight subjects, D2 was 4 mm and the FMD was 25% (Fig. 1a and b).

Table 2 shows the characteristics of the rheumatoid arthritis group in which the diameter of the brachial artery before the induction of ischemia (D1) was 4.3 mm in 10 subjects, after the release of ischemia (D2) 4.3 mm, the FMD was 0%. D1 was 4.1 mm in eight subjects, D2 was 4.3 mm and FMD was 4.8%. D1 was 3 in three subjects, D2 was 3.2 mm and the FMD was 6.6%. D1 was 3 in five subjects, D2 was 3.4 mm and the FMD was –96.6% (Figs. 2a and b, 3a and b, 4a and b).

So, the higher the numeric value of the FMD, the better the endothelial function.

The CIMT in the control group was 0.44 mm in eight persons, 0.47 mm in nine persons, and 0.35 mm in three persons (Fig. 1c) Table 3.

The CIMT in the rheumatoid arthritis patients was 0.50 mm in 10 persons, 0.54 mm in nine persons, and 0.56 mm in seven persons (Figs. 2c, 3c and 4c) Table 4.

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<th>Table 2</th>
<th>The brachial artery diameter and FMD in the rheumatoid arthritis patients.</th>
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<tr>
<td>Number</td>
<td>D1 (mm)</td>
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<tr>
<td>10</td>
<td>4.3</td>
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<td>8</td>
<td>4.1</td>
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Fig. 1b  The post-occlusion diameter of brachial artery in the same person = 4 mm, FMD 25% denoting good endothelial function.

Fig. 1c  The carotid intima media thickness 0.44 mm.

Fig. 2a  The basal diameter of the brachial artery in a patient with rheumatoid arthritis = 4.3 mm.
4. Discussion

Rheumatoid arthritis is associated with excessive cardiovascular mortality [6]. Almost half of all deaths in rheumatoid arthritis results from cardiovascular causes [7]. Therefore, it may be suggested that the main cause of mortality and morbidity is ischemic heart disease in patients with RA [7]. Discovery of early interventions in RA disease that might influence atherosclerotic progression are essentials to determine approaches that could in turn reduce the subsequent risk of cardiovascular mortality [8,9]. CIMT is a known strong predictor of cardiovascular events in the general population [10], and has been predominantly reported in the literature on patients with RA [11]. The results from our study show that the CIMT has a high predictive value for the development of CVD. Our results were the same as Gonzalez-Juanatey C et al. [12] in which the presence of subclinical atherosclerosis, manifested by increased value of CIMT is consistent with the high rate of silent ischemic heart diseases and sudden cardiac death observed in RA patients. Van Sijl AM et al [13] proved in their study that CIMT is frequently used to identify the population at elevated cardiovascular risk. [17] The results of our study implicate that the mean CIMT of the common carotid artery was significantly higher in RA patients than in healthy subjects. Van Sijl AM et al [13], found that the CIMT difference between RA patients and the control subject may be very small as in Higgins JP et al. [14] and other studies such as Kumeda Y et al. [15] & Mahajan V et al. [16] found a greater difference. Finally, Van Sijl AM et al [13] stated that the variation in ultrasound protocols for determining CIMT between all studies is an important observation but also complicates the interpretation of the individual study results. Still, they think that the differences in ultrasound protocols or in other methodological aspects are unlikely to have caused a systematic bias toward under- or overestimation of CIMT difference between RA patients and control. So, US scanning of CIMT has been shown to be an accurate method for estimating cardiovascular risk.

Fig. 2b  The post-occlusion diameter of brachial artery in the same person = 4.3 mm, FMD 0% denoting poor endothelial function.

Fig. 2c  The carotid intima media thickness in the same person 0.72 mm.

Fig. 3a  The basal diameter of brachial artery in a patient with rheumatoid arthritis = 4.1 mm.
RA appears to be associated with accelerated atherosclerosis, the mechanisms involved are not clear, but may include endothelial dysfunction mediated by systemic inflammation. Our study demonstrates that patients with RA can also present endothelial dysfunction which may be the earliest event in the atheromatous lesion, so its evaluation is a promising tool for the estimation of coronary affection. Castro PT et al. (19) study mentioned that FMD allows an adequate evaluation of endothelial behavior and reflects the coronary endothelial function and behavior, in spite of that the ideal method for diagnosing endothelial dysfunction has not been established yet. Our study coincides with those of Schroeder S et al. (20) in which the age of the patient does not affect the endothelial function evaluation with FMD. We have found no significant difference in the different age groups of patients and the control group regarding the FMD. Like the present study, other studies like Hurlimann D et al. (21) have found a significant endothelial dysfunction in patients with autoimmune disease like RA by means of FMD. The presence of systemic inflammation predisposes to atherosclerosis, affecting the endothelial function and decreasing the production of nitric oxide by the endothelium. This decrease in the nitric oxide production leads to a smaller arterial dilatation upon induced ischemia. Quyyumi AA (22) affirms that systemic inflammation markers like FMD, CIMT and pulse wave analysis arise as a method for evaluating the atherosclerosis risk. He recommends the inclusion of these methods in randomized study for screening and diagnosis of cardiovascular risk. Considering that a high level of systemic inflammation affects the endothelial function, inflammation markers like FMD may provide a better evaluation for the cardiovascular risk in patients with RA (23). In our study, we demonstrate that the FMD and

![Image](122x577 to 462x738)

**Fig. 3b** The post-occlusion diameter of brachial artery in the same person = 4.3 mm, FMD 4.8% denoting poor endothelial function.

![Image](108x81 to 476x216)

**Fig. 3c** The carotid intima media thickness in the same person 0.64 mm.
CIMT are promising methods for the evaluation of RA and are very helpful for the prevention of vascular risk.

5. Conclusion

The results from the present study support the use of carotid US and endothelial function assessment by means of FMD as a useful tool to predict the increased risk of cardiovascular disease in patient with rheumatoid arthritis. We suggest that the carotid artery US should be performed for all patients with rheumatoid arthritis to establish the risk of cardiovascular complication which requires more aggressive therapy.

References

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