

# Subclinical atherosclerosis in rheumatoid arthritis patients of the Gulf Cooperated Council

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### ABSTRACT

**Objectives:** To assess the existence of subclinical atherosclerosis in the Gulf Cooperation Council (GCC) rheumatoid arthritis (RA) patients in comparison to age, gender and cardiovascular disease (CVD) risk factors matched controls.

**Methods:** A cross-sectional study, 100 RA patients and 150 age, gender and CVD risk factors matched controls were recruited between June 2019 and December 2019. Detailed history, physical examination, and ultrasound examination of the carotid arteries for the carotid intima-media thickness (cIMT) and for the presence of atheroma, had been carried out. Differences between RA and controls carotid structural changes were carried out using t-test and Chi-test.

**Results:** Patients with RA showed more sub-clinical atherosclerosis with thicker cIMT at  $0.60\pm 1.4$  versus  $0.56\pm 0.09$  mm, ( $p=0.03$ ). cIMT is a surrogate marker for the presence of atherosclerosis and a predictor for the cardiovascular disease progression. Rheumatoid arthritis patients had more carotid atherosclerotic plaque; 21 (21%) patients versus 6 (4%) healthy controls ( $p<0.001$ ).

**Conclusion:** Subclinical atherosclerosis is more prevalent among RA patients of the GCC than the control participants.

**Keywords:** carotid intima media thickness, rheumatoid arthritis, cardiovascular disease, atherosclerosis, inflammation, C-reactive protein

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Cardiovascular diseases (CVD) is the chief cause of mortality and morbidity in rheumatoid arthritis (RA). The traditional CVD risk factors had been found insufficient to justify the excess risk of CVD in RA. Therefore, non-traditional CVD risk factors had been suggested to have an elemental role in the risk of CVD in RA.<sup>1-3</sup> Information about the risk of CVD in the Gulf

Cooperation Council (GCC) RA patients are scarce. In a previous publication we reported that many traditional as well as non-traditional CVD risk factors interplay in influencing the carotid intima-media thickness (cIMT) in RA patients of the GCC.<sup>4</sup> Carotid intima-media thickness is an indicator for subclinical atherosclerosis and for future CVD.<sup>5</sup> A letter to editor about the study came with a comment of absence of a control group to show the difference between RA patients and the control subjects of the GCC in term of cIMT.<sup>6</sup> Therefore, in this study we are answering the raised questions of the cIMT differences between RA and the matched control in age, gender and CVD risk factors. As well, this is the first time to look at the presence of carotid atheroma among RA patients of the GCC countries.

**Methods.** In a cross-sectional study, we recruited 100 RA patients fulfilling the ACR/EULAR 2010 criteria for classification of RA, 150 gender-aged and CVD risk factors matched control participants. The study had been conducted in the main federal hospital in Dubai, United Arab Emirates (UAE), between June 2019 and December 2019. The study had been conducted in concordance with the Declaration of Helsinki; the Research Ethics Committee, at the Ministry of Health and Prevention of UAE approved the study, and a written informed consent was attained from all the study participants. Detailed history, physical examination, laboratory investigations and US examination for the cIMT and carotid atheroma had been carried out for all the participants.

We excluded participants of less than 18 years old, participants with other autoimmune rheumatic diseases, diabetic (classified as present if participants had been diagnosed by a physician or were taking anti-diabetic medications at the time of the study), hypertensive (determined by physician diagnosis or by patient's use of anti-hypertensive medication), dyslipidemia (determined by physician diagnosis or by patient's use of lipid lowering medications), and patients with previous/current CVD, stroke or transient ischemic attack (defined by physician notes or if the participant was on anti-ischemia/infarction medications).

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**Table 1** - Demography, disease characteristics, and carotid ultrasound findings of 100 rheumatoid arthritis (RA) patients and 150 age-gender matched control subjects.

Demographic characteristics	Control	RA patients	P-value	Confidence interval
Male:female ratio	30 (20):120 (80)	16 (16):84 (84)	0.41	-
Age (years) (mean±SD)	49 ± 13	47 ± 16	0.23	47 - 50
Males mean age (years) (mean±SD)	52 ± 15	52 ± 19)	0.93	47 - 57
Smoking	15 (10)	8 (8)	0.09	-
<b>RA characteristics</b>				
RA duration (years) (mean±SD)	-	7 ± 4	-	-
Age at RA symptoms onset (years) (mean±SD)	-	40 ± 15	-	-
Age at RA diagnosis (years) (mean±SD)	-	42 ± 15	-	-
Tender joint count (of 28) (%)	-	12 (13)	-	-
Swollen joint count (of 28) (%)	-	4 (3)	-	-
RA nodules (%)	0 (0)	5 (5)	0.01*	-
Morning stiffness duration (minutes) (mean±SD)	-	62 ± 112	-	-
Rheumatoid factor positivity (%)	2 (1)	72 (72)	<0.001*	-
Rheumatoid factor level	8.08 (8.01)	55.60 (111.58)	<0.001*	15.65 - 40.15
Anti-CCP level (%)	0 (0)	47 (47)	<0.001*	-
ESR (mm/hr)	22.53 (16.50)	35.55(23.46)	<0.001*	24.69 - 30.57
CRP (mg/dl)	4.60 (5.02)	17.13 (34.09)	<0.001*	6.68 - 13.17
DAS 28-ESR (mean±SD)	-	4.3 ± 1.2	-	-
DAS 28-CRP (mean±SD)	-	3.4 ± 1.6	-	-
<b>Subclinical atherosclerosis</b>				
cIMT(mm) (mean±SD)	0.56 ± 0.09	0.60 ± 0.14	0.03*	0.56 - 0.60
Carotid atheroma (%)	6 (4)	21 (21)	<0.001*	-

Anti-CCP: anti-citrullinated peptide, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein,  
DAS-28 ESR: disease activity score-28 erythrocyte sedimentation rate, DAS-28 CRP: disease activity score- 28 C-reactive protein,  
cIMT: carotid intima-media thickness test

The control participants were recruited from the volunteers' database. The study had been explained through the phone and the participants who approved participation in the study were invited for a visit to the hospital for further clarification, to give a consent and to proceed with the participation in the study.

High-resolution B-mode US scanner with a 7.5 MHz linear probe (ESAOTE's MYLAB GAMMA MyLab™X8 Ultrasound System, Florence, Italy) was used to measure the cIMT. All the measurements had been carried out by a single sonographer. Patients were placed in supine position. The head of the scanned patient was turned away from the sonographer. The neck had been extended and mildly rotated. The cIMT measured as the distance between the leading edge of the intima-luminal and the media-adventitial interface at the wall of the carotid artery bilaterally. The measurement obtained 10 mm (1 cm) proximal to the bifurcation of the common carotid artery (bulb). Three images readings were obtained for each carotid artery.

The mean average of 6 measurements of the cIMT thickness were used for analysis.

We identified plaque as a focal broadening of the intima relative to adjacent segments, with protrusion into the carotid artery lumen that composed of either calcified deposits (hard plaque), non calcified deposits (soft plaque) or of a combination of both calcified and non calcified materials. Bilateral extra-cranial carotid arteries were lengthily scanned to recognize plaque. The plaque was considered present if pictured in the complete length of the vessel. The same investigator performed all cIMT measurements and analysis, and the carotid atheroma examinations.

**Statistical analysis.** Summary statistical analysis were presented as percentages for categorical data, and as mean (SD) for continuous variables. Unpaired t-test for the continuous variables and Chi-square test for the categorical variables were used for the comparison of differences between RA patients and the control participants.

A  $p$ -value of  $<0.05$  was considered significant. All statistical analysis was completed using Stata 9/SE statistical software (Stata Corp, College Station, Texas, USA).

**Results.** Among RA group, there were 84 females (84%) and 16 (16%) males. Among control participants there were 120 (80%) females and 30 (20%) males ( $p=0.41$ ). The mean age of RA participants was  $47\pm 16$  years, the mean age of the controls was  $49\pm 13$  years ( $p=0.23$ ).

The mean RA duration was  $7\pm 4$  years. The mean age for RA symptoms onset was  $40\pm 15$  years, but mean age for RA diagnosis was  $42\pm 15$  years. Inflammatory markers were high with CRP at a level of 17.13 (34.09) in RA versus 4.60 (5.02) mg/dl in the controls ( $p<0.001$ ) and the ESR level at 35.55 (23.46) in RA versus 22.53 (16.50) mm/hour in the controls ( $p<0.001$ ). Disease activity score-28 erythrocyte sedimentation rate (DAS 28-ESR) was 4.3 and disease activity score-28 C-reactive protein (DAS-28-CRP) was 3.4 among RA participants.

While rheumatoid factor (RF) positive status was detected in 72 (72%) of RA patients at a level of 55.60 (111.58) versus 8.48 (8.06) IU/ml ( $p<0.001$ ) in the controls, the anti-citrullinated peptide (anti-CCP) antibodies was detected in 47 (47%) of RA patients.

The investigation of subclinical atherosclerosis showed that RA patients had more subclinical atherosclerosis with thicker cIMT at  $0.60\pm 0.14$  mm compared to  $0.56\pm 0.09$  mm in the control group, ( $p=0.03$ ). The prevalence of atheroma was more in RA group, where 21% of RA patients had carotid atheroma versus 4% of the control participants ( $p<0.001$ ).

**Table 1** summarizes the demography, RA characteristics and the carotid artery US examination.

**Discussion.** Among RA, CVD is the most common cause of morbidity and mortality.<sup>7,8</sup> In this study, we looked for signs of subclinical atherosclerosis using carotid arterial ultrasound scanning in RA patients. Using US, cIMT or carotid plaque had been described as signs of atherosclerotic risk, and had been linked to CV consequence.<sup>2</sup> Others found that cIMT in RA patients is more thick than healthy controls, and it is affected by age, region and race.<sup>9</sup> Carotid intima-media thickness evaluates atherosclerotic risk and can provide evidence that is independent to other evidence that

can be obtained by measuring the traditional CVD risk factors. Non-invasive techniques like ultrasound measurement of cIMT can be valuable for CVD risk assessment at primary prevention level.

Current study indicates that RA patients of the GCC have increased atherosclerotic burden as demonstrated by increased cIMT and by more presence of carotid arterial plaque, with more prevalence of carotid atheroma. In the view of the inadequate data about RA in the region our study shed a light CVD in RA.

**Study limitations.** The majority of the study participants were females; accordingly, the study results cannot be generalized to the male population.

In conclusion, RA patients of the GCC region have an increased atherosclerotic burden. As cIMT represent early stage (subclinical) of atherosclerosis, it may have an important role in the prevention of CVD and controlling CVD risk factors in RA patients. Hence, reducing morbidity and mortality and improving life quality.

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