Original Article

Variables associated with subclinical atherosclerosis among rheumatoid arthritis patients of Gulf Cooperative Council countries

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ABSTRACT

الأهداف: تقييم أمراض القلب والأوعية الدموية (CVD) من سماكة الشريان السباتي الأوسط (cIMT) وعوامل الخطر المجمعة للأمراض القلبية الوعائية بما في ذلك وظائف البول التقليدية وغير التقليدية وتراكم الحديد، والنزيف لدى مرضى التهاب المفاصل الروماتويدي (RA) بدول مجلس التعاون الخليجي.

المنهجية: حصلنا على سماكة الشريان السباتي الأوسط من 216 مريض RA، غير مصابين بأمراض تصلب الشرايين. ثم أجرينا دراسة العلاقة بين cIMT وعوامل الخطر المحتملة لأمراض CVD باستخدام تحليل الانحدار.

النتائج: لوحظ أن متوسط cIMT هو 0.11±0.58مم. كان متوسط العمر 48 ± 13 عام. كشف التحليل أحادي المتغير ارتباط إيجابي (P>0.05) بين cIMT وكلاً من العمر، ومؤشر كتلة الجسم، وضغط الدم الانقباضي (SBp)، وضغط الدم الانبساطي، والبروتين التفاعلي (CRP)، والدهون الثلاثية (TG)، والبروتين الدهني منخفض الكثافة (LDL)، ومعدل ترسيب كرات الدم الحمراء (ESR)، والهيموغلوبين (Hb)، وحَجْمُ الكرَيّات الحُمْر المُكدَّسَة (Hct)، ومعدل حجم الخلية ،و الصفائح الدموية، والوحيدات، والخلايا الحمضية، والفيريتين ، والكرياتينين، وحمض اليوريك. وقد لوحظ علاقة سلبيه بين cIMT وسرعة الترشيح الكبيبي (GFR)، والترانسفيرين، والبروتين الشحمي المرتفع الكثافة. اظهر تحليل الانحدار الخطي المتعدد وجود علاقة إيجابية بين cIMT والعمر ، وLDL، والخلايا الحمضية، وSBp ، وESR، وعلاقة سلبية مع GFR و الترانسفيرين.

الخلاصة: في هذه الدراسة، وجدنا أن الخلايا الحمضية، وانخفاض الترانسفيرين، عوامل مرشحه محتمله من عوامل الخطر للإصابة بالأمراض القلبية الوعائية في مرضى التهاب المفاصل الروماتويدي. لاحظنا كذلك أن مستوى السكر في الدم أثناء الصيام عامل خطر مهم في مرضى التهاب المفاصل الروماتويدي المصابين بالسكري وغير المصابين. واشتملت عوامل الخطر الأخرى للأمراض القلبية الوعائية في مرضى التهاب المفاصل الروماتويدي من دول مجلس التعاون الخليجي على كبر السن، وارتفاع SBp، وESR، وLDL، وانخفاض GFR على غرار الشعوب الدوليه الأخرى.

Objectives: To evaluate the cardiovascular disease (CVD) as demonstrated by carotid intima-media thickness (cIMT) and the cluster risk factors of CVD including traditional and non-traditional, urinary functions, iron buildup, and hemorheology in rheumatoid arthritis (RA) patients of Gulf Cooperative Council (GCC) countries.

Methods: Carotid intima-media thickness was obtained from 216 RA patients, free of atherosclerotic diseases. The correlation between cIMT and the possible CVD risk factors was carried out using regression analysis.

Results: The mean cIMT was observed as 0.58±0.11 mm. Mean age was 48±13 years. Univariate analysis revealed a positive association (p<0.05) between cIMT and age, body mass index, systolic blood pressure (SBp), and diastolic blood pressure, c-reactive protein (CRP), triglycerides (TG), low-density lipoprotein (LDL), erythrocyte sedimentation rate (ESR), hemoglobin (Hb), hematocrit (Hct), mean cell volume, platelet, monocytes, eosinophils, ferritin, creatinine, and uric acid. Negative relationship was observed between cIMT and glomerular filtration rate (GFR), transferrin, and high-density lipoprotein. Multiple linear regression analysis exhibited a positive association between cIMT and the age, LDL, eosinophil, SBp, and the ESR, whereas, negative connection with the GFR and transferrin.

Conclusion: In this study, we found that the eosinophils, and low transferrin, are the potential candidates for the CVD risk factors in RA patients. Fasting blood glucose level was also observed to be a significant risk factor in diabetic as well as non-diabetic RA. The remaining CVD risk factors in RA patients of GCC countries including older age, high SBp, ESR, LDL, and low GFR were similar to the international population.

Keywords: carotid intima-media thickness, rheumatoid arthritis, cardiovascular disease, atherosclerosis, inflammation, c-reactive protein, ischemic heart disease

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Patients with rheumatoid arthritis (RA) have an augmented risk of cardiovascular disease (CVD) compared to the general population.[1-3] In addition to traditional and non-traditional CVD risk factors, the systemic inflammation in RA increases the probabilities of CVD. However, still, there is a gap in the literature about what are the mechanisms involved and how these factors add to the CVD risk. In comparison to the general population, the traditional CVD risk factors behave differently in RA patients.[4] Possibly, there could be a geographical variation of these risk factors across the globe. Realizing that the pathogenesis of CVD is complex; knowledge about determinants are needed. Therefore, we suggested CVD risk factors that have been identified by other researchers to be related to CVD in general, might contribute to the CVD process in RA. These risk factors include altered hemorheological parameters and iron accumulation.[5]

Cardiovascular disease is part of a larger process of atherosclerosis, which is a slowly progressive and diffuse change to the arterial tree. Modern ultrasound techniques are useful for the evaluation of both atherosclerosis-associated anatomical and functional changes. Carotid intima-media thickness (cIMT) is a non-invasive ultrasonic good surrogate marker of the presence of atherosclerosis and probable stages of atherosclerosis. A single cIMT assessment is having similar significance to the frequently used risk factors for the purpose of estimation of CVD and coronary heart disease (CHD).[6] Furthermore, cIMT measurement could serve as a graded marker for CVD and as a standard marker of the burden of atherosclerosis.[7]

Identifying variable CVD risk factors in relation to RA is of great importance for primary prevention of CVD and therefore reducing associated mortality and morbidity. Hence, the objective of this study was to evaluate the rate of atherosclerosis and its connection with CVD risk factors including traditional and non-traditional, RA inflammatory markers and RA-disease activity scores. Moreover, we also observed the urinary function, iron study, and the hemorheology effect on the cIMT.

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Methods. We conducted a cross-sectional study and included 216 patients who completed the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) standards for the classification of RA.[8] The patients had been recruited through a main tertiary federal hospital in Dubai, United Arab Emirates (UAE) over a period of 5 years (2013-2018).

Compliance with ethical standards. Humans' subjects were involved in the study. All procedures accomplished in the study were according to the ethical values of the institutional and the national research committee and with the 1964 Helsinki declaration and following amendments. The study received ethical approval from the Central Research Ethics Committee of the Ministry of Health and Prevention of the United Arab Emirates. Written ICF was obtained from all participants included in the study.

Medical histories of the patients were recorded by reviewing the electronic files. Information obtained included age, status of rheumatoid factor (RF), rheumatoid factor level (NR: 0.0-14 IU/ml), present medications, co-morbidities (namely, hypertension, diabetes, dyslipidemia, gout, thyroid, and renal illnesses), smoking status (current/past smoking history). Patients were excluded if they had a smoking history, history of CVD, diabetes, hypertension, thyroid, renal disease, gout, patients on diuretics medications, and pregnant women. Hypertension was defined as the use of antihypertensive medications or as recorded blood pressure (BP) ≥140/90. Gout was defined as a recorded clinical diagnosis or as the use of hypouricemic agents. Diabetes was defined as the use of diabetic medications (oral or injections) or had been diagnosed with diabetes mellitus. Thyroid disease was defined as the use of thyroid medications or had been diagnosed as a case of thyroid problem (hypo or hyperthyroidism).

Laboratory investigations were carried out within one week of cIMT ultrasound (US) measurement. The patients were subjected to the detailed physical investigation including joints swelling and tenderness. Systolic blood pressure (SBp) and diastolic blood pressure (DBp) were recorded in the right upper arm in a seated position with an automatic oscillometric BP recorder. Standing height and weight were measured to calculate the body mass index (BMI) using the following formula: BMI = weight (kg)/height (meter)^2.

Disease activity scores for 28 joints (DAS-28) were measured using erythrocyte sedimentation rate (ESR), (normal range [NR]: 0.0-30 mm/hour) and c-reactive protein (CRP), (CRP; 0.0-4.0 mg/L).

Rheumatoid factor positivity and level obtained using immunoturbidimetric technique (NR: 0.0-14 IU/ml). Fasting blood sample was collected for measurement of fasting glucose level (NR: 4.6-6.4 mmole/L), total cholesterol (NR: 2.0-2.5 mmole/L), low-density lipoprotein (LDL) (NR: 0.0-2.5 mmole/L), high-density lipoprotein (HDL) (NR: 1.0-1.6 mmole/L), triglycerides (TG) (NR: 0.4-1.9 mmole/L), urea (NR: 0.0-8.3 mmole/L), creatinine (NR: 44-133 µmole/L), serum uric acid (SUA) (NR: 155-476 µmole/L), iron study parameters (iron, ferritin, transferrin), hemorheology, erythrocyte sedimentation rate (ESR), and CRP. Glomerular filtration rate (GFR) was measured by the modification of diet in renal disease equation (MDRD).

Carotid intima-media thickness US measurement. Carotid intima-media thickness US measures acquired through a real-time US scanner, armed with a 7.5 MHz linear probe. All the measurements were recorded by a single sonographer. Patients were positioned in the supine position, with the head turned away opposite to the sonographer, and little extended neck with slight rotation. The length between the intima-luminal interface and the media-adventitial interface was considered as the cIMT and the thickness was recorded in the far wall of both carotid arteries, at a place approximately one cm proximal to the carotid artery bifurcation. Three were images captured for each side, and the averages of the 6 measures used for statistical applications.

Statistical analysis. Stata 9/SE statistical software (Stata Corp, College Station, Texas, USA) used for statistical analysis. The summary of the statistical analysis results were expressed as percentages for categorical variables, whereas mean±SD for continuous variables. Before applying stats, the data for cIMT were logarithmically transformed. The correlation among cIMT and other variables were analyzed using simple linear regression analysis considering cIMT as a dependent variable (outcome). Covariates; independent variables were the traditional CVD risk factors, RA related inflammatory markers (ESR, and CRP), DAS, urinary function, iron study parameters, and hemorheology parameters.

In order to determine whether independent associations present between cIMT and other variables of the study backward multiple linear regression (MLR) models were fitted in the analysis. The multivariate model analysis was performed in a way that included all the independent variables that were significantly associated with the cIMT in the univariate models. A $p<0.05$ was considered statistically significant.

Results. In this study, we included 216 patients. The demographic features and the RA characteristics, iron study and renal function of the participant are listed in Table 1. The average cIMT was found to be 0.58±0.11 mm (minimum: 0.28, maximum: 0.98). Whereas, mean age was recorded as 48±13 years (48±12 years for females, 50±16 years for males, p=0.279). Rheumatoid factor was found to be positive in 168 (78%) patients, and the mean RF level was 56±109 IU/ml. The mean ESR was 28.904±22 mm/hour, and CRP was 10.116±25, 452 mg/dL. Cardiovascular disease risk factors analysis showed an SBp 126±20, 526 mmHg and DBp 74.890±11.341 mmHg. Mean BMI was 30.361±6.316 kg/m^2. The univariate regression analysis (Table 2) exhibited a positive linear association between cIMT and age of the patients (p=0.001), hemoglobin (Hb) (p=0.006), hematocrit (Hct) (p=0.006), mean cell volume (MCV) (p=0.027), mean cell hemoglobin (MCH) (p=0.04), platelet (p=0.000), monocytes (p=0.02), eosinophils (p=0.011), and ESR (p=0.04). Furthermore, positive linear correlation also observed between cIMT and creatinine (p=0.002), uric acid (p=0.002), TG (p=0.033), LDL (p=0.002), CRP (p=0.000), ferritin (p=0.000), body weight (p=0.018), BMI (p=0.026), SBp (p=0.000), and DBp (p=0.001). Whereas, transferrin (p=0.001), HDL (p=0.000), GFR (p=0.024) were found with negative linear relationship with cIMT. The data for adjusting confounding variables carried out by comprising all independent variables showing a significant linear correlation with the cIMT in the univariate analysis into a multivariable regression analysis (MLR) are presented in Table 3. The MLR analysis exhibited a positive linear relationship between IMT and age (p=0.000), LDL (p=0.003), eosinophils (p=0.025), SBp (p=0.004), and the ESR (v=0.016). In addition to this, the MLR analysis demonstrated a negative linear association between cIMT and GFR (p=0.02), and transferrin (p=0.000). The R2 value of the regression model was found to be 0.65.

Discussion. Atherosclerotic diseases may remain asymptomatic for many years, but even on the first appearance of symptoms, it becomes fatal and life-threatening. Therefore, early diagnosis and prevention of atherosclerosis turned out to be essential targets in the field of CVD. Presently the non-invasive B-mode US considered ideal for the screening of CVD. Using US techniques, evidence of increased sub-clinical atherosclerosis in RA subjects has been shown in several studies but the correlation of cIMT and each of urine function parameters, and blood rheology has been explored in only few studies. This study investigated

Table 1 - Demographic details, rheumatoid arthritis characteristics, iron study, renal function, Carotid intima-media thickness (cIMT) and hemorheology of 216 rheumatoid arthritis (RA) patients.

Demographic details	Mean ± SD
Male:Female (ratio)	37:179
Age	48 ± 13
Male age	50 ± 16
Female age	48 ± 12
BMI (kg/Ht^2)	30.361 ± 6.316
RA characteristics	
ESR (mm/hr)	28.904 ± 22.156
CRP (mg/dl)	10.116 ± 25.452
DAS-ESR	5.136 ± 1.548
DAS-CRP	4.451 ± 1.518
Tender joint count (of 28)	15 (11)
Swollen joint count (of 28)	4 (5)
Rheumatoid factor level	56 (109)
Rheumatoid factor positive	168 (78)
Iron study	
Ferritin	70.940 ± 84.550
Transferrin	265.987 ± 71.836
Iron	11.642 ± 5.390
Renal function	
Creatinine	57.677 ± 18.354
Uric acid (µmol/L)	282.322 ± 91.234
Urinary protein (mg/L)	151.568 ± 230.392
GFR (ml/min)	123.474 ± 34.711
Urea	4.410 ± 5.243
Traditional CVD risk factors	
Systolic blood pressure (mmHg)	126 ± 20.526
Diastolic blood pressure (mmHg)	74.890 ± 11.341
Glucose fasting	7.097 ± 9.820
Glycosylated hemoglobin (mmol/mol)	6.492 ± 1.640
Cholesterol	4.603 ± 0.960
Low-density lipoprotein (mmol/L)	2.842 ± 0.966
Triglycerides (mmol/L)	1.278 ± 0.753
High-density lipoprotein (mmol/L)	1.332 ± 0.512
Atherosclerosis parameter	
Carotid intima-media thickness	0.579 ± 0.112
Hemorheology	
White cell count (0^{-3}/mcl)	7.338 ± 2.725
Hemoglobin (g/dl),	12.371 ± 1.681
Hematocrit	38.232 ± 4.769
Mean cell volume	83.837 ± 8.605
Mean cell hemoglobin	27.334 ± 4.113
Platelet	271.424 ± 76.402
Monocyte (10^{-3}/mcl)	7.716 ± 2.511
Lymphocyte (0^{-3}/mcl)	34.471 ± 10.718
Basophil (0^{-3}/mcl)	2.687 ± 1.831
Neutrophil (0^{-3}/mcl)	54.778 ± 12.160
Eosinophil (10^{-3}/mcl)	2.687 ± 1.831

Values are presented as numbers and percentages (%). RA: rheumatoid arthritis, BMI: body mass index, ESR: erythrocyte sedimentation rate, CRP: c-reactive protein, DAS: disease activity score, GFR: glomerular filtration rate

the cIMT in RA patients of the GCC population, and none of them observed at each of traditional, inflammatory markers, disease activity score, urinary functions, iron status, and blood rheology in the same group of RA investigated the cIMT in RA patients of the GCC population, and none of them observed at each of traditional, inflammatory markers, disease activity score, urinary functions, iron status, and blood rheology in the same group of RA.

Carotid intima-media thickness and age of RA patients. Our results showed a linear positive correlation with the RA patients' age and the cIMT. This finding agrees with many previous reports that showed the effect of the age of RA patients on cIMT.[3] Multivariate modeling indicated that a sizeable age-related effect remained, in addition to many traditional and non-traditional CVD risk factors. Therefore, it is likely that increased cIMT is not merely an isolated age effect. Although age is not amenable to RA treatment; however, many other risk factors associated with age could be altered and modified by available medications.

Carotid intima-media thickness, Hb, Hct, and MCV. Complete blood count (CBC) and hemorheological parameters symbolize valuable, economical, and extensively accessible laboratory tools. Interestingly, CBC and hemorheological parameters have been reported as good measures for assessing the management and prognosis of various CVD including CHD, heart failure (HF), stroke, arrhythmias, and hypertension.[9]

Several studies evaluated the relationship between CVD and each of Hb and Hct level. These studies have made known that anemia (low Hb concentration) and polycythemia (high Hb concentration) are autonomous CVD risk factors in the common populace.[10-12] Others reported that low or high Hb levels are related to raised CVD and all-cause mortality. Whereas attaining and maintaining Hb levels in the standard range reported to reduce the all-cause mortality. Smith et al,[13] reported a positive connection between Hb concentration and traditional CVD risk factors including total cholesterol, fasting glucose, smoking status, BMI, and BP, after the adjustment for age. The relationship between Hb and CVD persisted even after the fine-tuning of data for these traditional CVD risk factors.[13]

Similarly, either low or high Hct (percentage of red blood cells) levels are associated with an increased CVD risk.[3] Some studies found elevated Hct as a predictor of atherosclerosis incidence, unstable angina, and myocardial infarction as an independent risk of CVD morbidity and mortality.[15,16] The Framingham Heart Study described the association between high Hct and CVD occurrence in females after adjusting for multiple CVD risk factors.[17]

Increased Hb or Hct level results in augmented blood viscidness and blood thickness. The elevated

Table 2 - Multivariatelinear regression analysis of the relationship between cIMT, selected RA features, traditional CV risk factors, urinary parameters and hemorheologyin 2016 patients with RA.

Variables	R^2	β coefficient	Standard error	t	*P*-value	Confidence interval
Age, (years)	0.33	0.005	0.000	10.04	0.000	0.004-0.006
Systolic blood pressure (mmHg)	0.11	0.002	0.000	4.62	0.000	0.001-0.003
Diastolic blood pressure (mmHg)	0.06	0.002	0.001	3.29	0.000	0.001-0.004
RBC (10 (6)/mcL)	0.00	0.011	0.014	0.75	0.457	-0.018-0.039
Hemoglobin (g/dl)	0.05	0.014	0.005	2.79	0.006	0.004-0.024
MCH (pg)	0.02	0.005	0.002	2.02	0.040	0.000-0.009
MCV (fL)	0.03	0.002	0.001	2.23	0.027	0.000-0.004
Hct (%)	0.04	0.005	0.002	2.77	0.003	0.001-0.009
MCV (fL)	0.03	0.002	0.001	2.23	0.027	0.000-0.004
Platelet (10 (3)/mcL)	0.07	-0.000	0.000	-3.64	0.000	-0.001-0.000
WCC (10 (3)/mcL)	0.02	0.005	0.003	1.68	0.095	-0.001-0.010
Neutrophil (10 (3)/mcL)	0.00	-0.000	0.001	-0.72	0.475	-0.002-0.001
Lymphocyte (10 (3)/mcL)	0.00	0.000	0.001	0.08	0.938	-0.001-0.001
Monocyte(10 (3)/mcL)	0.03	0.010	0.004	2.29	0.023	0.001-0.019
Eosinophil (10 (3)/mcL))	0.04	0.011	0.004	2.57	0.011	0.002-0.019
Basophil (10 (3)/mcL)	0.01	0.006	0.028	0.22	0.823	-0.049-0.061
Weight measured (kg)	0.03	0.001	0.000	2.39	0.018	0.000-0.002
Body mass index (kg/ht^2)	0.03	0.003	0.001	2.26	0.026	0.004-0.006
ESR (mm/hr)	0.02	0.001	0.000	2.01	0.040	0.000-0.001
CRP (mg/dl)	0.08	0.001	0.000	3.95	0.000	0.001-0.002
Creatinine (mmol/L)	0.05	0.001	0.000	3.14	0.002	0.000-0.002
Uric acid ((µmol/L)	0.05	0.000	0.000	3.15	0.002	0.000-0.001
Urinary protein (mg/L)	0.23	0.000	0.000	5.11	0.000	0.000-0.001
GFR (ml/min)	0.03	-0.001	0.000	-2.28	0.024	-0.001- -0.000
LDL (mmol/L)	0.06	0.028	0.009	3.15	0.002	0.010-0.045
HDL (mmol/L)	0.09	-0.070	0.017	-4.09	0.000	-0.103- -0.036
Cholesterol	0.01	0.004	0.009	0.41	0.684	-0.021-0.014
Triglyceride (mmol/L)	0.03	0.023	0.011	2.15	0.033	0.002-0.044
Glucose fasting (mmol/L)	0.02	0.001	0.001	1.71	0.080	-0.000-0.003
Iron (unit)	0.01	0.000	0.002	0.11	0.091	-0.004-0.004
Ferritin (mcg/L)	0.13	0.000	0.000	4.06	0.000	0.000-0.001
Transferrin (mg/dl)	0.12	-0.001	0.000	-3.53	0.001	-0.001- -0.000

RA: rheumatoid arthritis, cIMT: carotid intima media thickness, CV: cardiovascular, RBC: red blood cell (10 (6)/mcL), MCH: mean cell hemoglobin, MCV: mean cell volume, Hct: hematocrit (%), WCC: while cell count, ESR: erythrocyte sedimentation rate, CRP - C-reactive protein, GFR - glomerular filtration rate, LDL - low density lipoprotein, HDL - high density lipoprotein.

Table 3 - Multivariate linear regression analysis of the relationship between cIMT, selected RA features, traditional CV risk factors, urinary parameters and hemorheologyin 216 patients with RA.

Variables	β coefficient	SE	t	*P*-value	CI
Age, (years)	0.004	0.001	5.28	0.000	0.003-0.006
Systolic blood pressure (mmHg)	0.002	0.001	3.00	0.004	0.001-0.003
LDL (mmol/L)	0.033	0.010	3.19	0.003	0.012-0.053
Glucose fasting (mmol/L)	0.010	0.005	2.20	0.033	0.001-0.020
ESR (mm/hr)	0.001	0.001	2.51	0.016	0.002-0.008
Eosinophil (10 (3)/mcL)	0.013	0.005	2.32	0.025	0.002-0.023
Transferrin (mg/dl)	-0.001	0.000	-4.24	0.000	-0.001- -0.000
GFR (ml/min)	-0.001	0.000	-2.38	0.022	-0.001- -0.000

RA - rheumatoid arthritis, cIMT - carotid intima media thickness, CV - cardiovascular, SE - standard error, CI - confidence interval, LDL - low density lipoprotein, ESR - erythrocyte sedimentation rate, GFR - glomerular filtration rate.

blood thickness alters blood circulation, consequently increasing peripheral resistance which leads to slow blood circulation to the organs as well as slow oxygenation.[18,19] Furthermore, it upsurges atherogenesis, stimulates plaque rupture, and thus finally leads to ischemia.[20] Moreover, elevated Hct level triggers platelet activation as well as oxidative stress phenomenon by discharging adenosine diphosphate (ADP) in reaction to iron build up.[21]

In addition to the Hb and Hct levels, the mean corpuscular volume (MCV) has been reported to be correlated with CVD risk in a variety of populations.[22,23] Our study extending the knowledge about hemorheology alteration as a CVD risk in RA patients. Our results showed a positive correlation between the Hb concentration, Hct level, and MCV with CVD as manifested by cIMT for the first time in the RA population. The combination of Hb, Hct, MCV levels, and CVD risk may empower the ability for timely detection of CVD.

Carotid intima-media thickness and platelet. Platelets are another component of hemorheology that has been investigated as a cause and as a marker of CVD. Platelet count has been reported to be linked with CVD deaths in a population-based cohort study.[24] On the other hand, platelet functional abnormality has also been studied. Subjects with an ischemic heart ailment and with coronary artery disease (CAD) risk factors are reported to have abnormal and sensitive platelets.[25] Therefore, it can be established that platelet aggregation and endothelial damage are associated with the etiology of atherosclerosis. Products discharged from platelets through the accumulation process may trigger arterial spasm.[25] Our study revealed that platelet count is connected with cIMT in a positive linear design, supporting a possible role for platelets in CVD.

Carotid intima-media thickness and white cell count (cIMT and monocytes). Several studies have stated that an elevated leukocyte count is a robust and impartial CVD risk factor.[26,27] In other studies, monocyte count confirmed to be correlated with the incidence and development of subclinical cIMT, to foresee the untimely manifestation of a coronary incidence, to be related to BMI, clustering of metabolic syndrome, CVD history, atherosclerotic plaque instability and rupture, and that particular monocyte sub-classes control hyper-cholesterolemia-related monocytosis and produce precisely to macrophages in atheroma.[28-35]Monocyte and monocyte-originated macrophages impart a vital role in the initial stage of atherogenesis and the progression of atherosclerosis.[36,37] Olivares et al,[31] reported that the risk of coronary heart disease rose 1.15 times if there was an increase of 100 cells/mm^3 in monocyte count. Following previously published results, our results emphasize the significant correlation between the monocytes and cIMT. Moreover, our study extends this relation to apply to the CVD risk among RA patients.

Carotid intima-media thickness and eosinophils. Prentice et al,[38] reported a similar relation between CVD and other parameters of white cell count (WCC); eosinophil and neutrophils count. Eosinophil count and the ratio of eosinophil to leukocyte has been materialized as unique biomarkers in CAD patients for risk classification in patients with CAD. Eosinophils impart a key role in vasoconstriction, endothelial malfunction, thrombosis, and swelling.[39,40] Other studies demonstrated that eosinophils are connected with coronary artery calcification, stent restenosis, slow coronary flow, stent thrombosis and acute coronary disorders.[41]

On the other hand, there is a published report claiming that elevated eosinophils level is not autonomously correlated with the incidence and magnitude of CAD. However, chances are more that it is linked with the most important cardiovascular risk factors.[42]

The cIMT in our RA groups was significantly associated with the eosinophils count in the univariate linear regression. This relationship was found to be maintained even when adjusted for the other CVD confounding factors in the multivariate analysis.

Carotid intima-media thickness and iron status. Iron is vital for numerous metabolic pathways and physiological processes. The maintenance of iron homeostasis is essential, and an increase or a decrease in its level can be harmful to the human body. Iron overload has been identified as a CVD risk factor.[43]

Transferrin is a blood-plasma glycoprotein that transports iron through the blood to various tissues, while ferritin is an iron-storage marker and has a role in iron distribution, propagation, angiogenesis, and as well as in immune-suppression.[44] The synthesis of ferritin which serves as an acute-stage protein is initiated by cytokines, and this could be the reason for its increased levels in diseases involving inflammation.[45] Although some studies reported a positive association between elevated ferritin levels with CVD, and cIMT.[46,47] Ferritin level ≥200 mg/L reported being associated with a 2.2 times rise in the probability of acute myocardial infarction even when adjusted for additional risk factors.[48] However, there are few reports failed to demonstrate any connection between ferritin concentrations and CVD.[49,50] These conflicting results of ferritin association with CVD could be explained by

large variability in iron stores estimates, which included serum iron, serum ferritin, serum transferrin, and the diverse methods in the diagnosis of atherosclerosis.[51,52]

Our study results agree to the concept of increased risk of CVD with excess iron overload as it is showing a positive and linear association between cIMT and ferritin, as well as transferrin levels. The association with the transferrin had been maintained in the MLR after adjustment with the additional CVD risk factors. This is the first study of its kind to show this finding in RA patients The positive association is supported by the capability of iron accumulation to catalyze the creation of free radicals and a reduction of antioxidant levels in plasma through the promotion of lipid peroxidation. Oxidized LDL enhances lipid accumulation in the arterial endothelial and smooth cells, and stops macrophages from exiting the arterial wall. Thus, promote atherosclerosis and increases the risk of ischemic cardiovascular events.[43,53,54]

The sensitive, rapid, validated, and inexpensive assay makes ferritin and transferrin a possible future CVD biomarker, with potential implications for public health. These findings require further investigation in a more extensive multi-center study.

Carotid intima-media thickness and renal function. Sub-clinical renal abnormalityis prevalentin RA and acquaintances with CVD risk.[55,56] We have reported that sub-clinical renal activity in concurrence with the traditional along with non-traditional CVD risk factors affects combinedly to hasten atherosclerosis in RA patients.Additionally, GFR has a strong relationship with many traditional and non-traditional CVD risks in the RA population.[57] Furthermore, the presence of SUA in atherosclerotic plaques is considered to play a significant role in the manifestation of atherosclerosis.[58] Moreover, we demonstrated previously of a positive linear association among SUA and cIMT in RA.[59] However, other investigators reported that SUA is associated with many CVD risk factors including diabetes mellitus, hypertension, hyperlipidemia and obesity.[59-62] The data of this study confirms our previous report that the sub-clinical renal function and the SUA lead to cardiovascular risk in RA.

Carotid intima-media thickness and traditional CVD risk factors TG, LDL, HDL, and BMI. Kroot et al,[63] found that hypertension is the most frequently reported co-morbid conditioning RA, followed by angina pectoris. Different mechanisms have been postulated to explain increased atherosclerosis in RA. One hypothesis is related to the co-integration observed between RA and traditional cardiovascular risk factors.[64] This integration might be evident in our study that showed cIMT is positively affected by the level of LDL and TG level and negatively with the HDL level. In addition to this, BP parameters, SBp and DBp; which are the significant determinants of arterial stiffness, showed to be positively associated with cIMT.

Several reports are available, mentioning that BMI some how influences the development and progression of RA.[4] There are inconsistent results about the high BMI effect on CVD; some reports suggested an augmented CVD risk in obese persons; however, others reported no such correlation to exist.[65,66] Nevertheless, most studies indicated that obesity and RA have a positive correlation especially in women.[67] In our study, we found a mean BMI as 30.316 (class 1 obesity), which can be attributed to the sedentary lifestyle of RA patients. The majority of our sample were female (83%). Our results are following the positive linear association between BMI and cIMT.

The reported results of this study about lipid profile, hypertension, and BMI with the cIMT, support many preceding publications, including our previous studies on RA patients.[1,3,59,68]

The results of the current study stress the concept of regular screening and rigorous management of hypertension, dyslipidemia, traditional cardiovascular risk factors. Additionally, the control of the inflammation is also essential as it synergistically augments the traditional CVD risks in RA patients.

Carotid intima-media thickness and inflammatory markers (ESR and CRP). Inflammation plays a crucial role in RA, and several newlines of evidence suggested that atherosclerosis has an essential inflammatory component.[69] The concept that inflammatory mediators are actively involved in the progression of vascular damage in RA. These findings are also supported by our study results, which demonstrated a positive and linear correlation amid cIMT and each of the CRP and ESR.

There is a necessary implication of this link, a significant portion of the risk for CVD contained in the inflammatory markers, particularly the CRP and the ESR, can be diagnosed, and the effects of interventions possibly monitored through anti-rheumatic medication. Besides, a large portion of the excess risk from CVD might be alleviated by interventions that reduce inflammation.

One strength of this study was the repetitive measurements of the far wall of left and right carotid arteries, so the chances of errors were high. Therefore, to minimize the reader's bias, variability, and noise we utilized selected and specific software for the automatic

measurement of cIMT.[70] Another strength was that we selected the far wall portion of the left and right carotid artery to measure as this segment was easy to approach and suitable for rhythmic measurements. Another strength of this study was the bigger sample size and the exclusion of participants with other diseases, and patients with smoking history.

Study limitations. The drawback of this study was that it was performed mainly on women (83% of the study sample), and consequently, the study results cannot be extrapolated to the male population. The opted design of the study was cross-sectional, which is well known for its process limitations. Further randomized studies with large sample size and with an equal proportion of males and females are needed to establish the cIMT as a screening for atherosclerosis in RA.

In conclusion, our findings suggest that attention should be given to the risks of CVD in RA patients in the GCC region. The presence and severity of inflammation as cardiovascular risk factors should be considered and treated, in addition to trying to correct the known modifiable cardiovascular traditional risk factors. Furthermore, attention shall be paid to sub-clinical renal impairment and alternation in iron status and hemorheology.

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