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ORIGINAL ARTICLE

Uric acid is independent cardiovascular risk factor, as manifested by increased carotid intima-media thickness in rheumatoid arthritis patients

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Abstract Rheumatoid arthritis (RA) is associated with increased cardiovascular disease (CVD) mortality and morbidity, due to the combined effects of traditional and non-traditional cardiovascular risk factors (CV). A serum uric acid (SUA) level has been suggested as one of the non-traditional cardiovascular risk factors. Cardiovascular risk can be assessed by looking at the subclinical atherosclerosis such as ultrasound (US)-measured carotid intima-media thickness (cIMT). This paper aimed to determine the role of SUA as a cardiovascular risk factor, along with the traditional cardiovascular risk factors and inflammation, among RA population. RA patients with no clinically evident CV or renal disease were studied. cIMT US, SUA, traditional cardiovascular, and inflammatory markers were obtained and correlated with cIMT. Among 53 RA patients (5 males, 48 females, mean age 48 ± 14 years), univariate linear-regression showed a positive linear relationship between cIMT and age ($p < 0.001$), age at RA symptoms onset and diagnosis ($p = 0.010$ and 0.003, respectively), number of cigarettes/day ($p < 0.001$), systolic and diastolic blood pressure ($p = 0.005$ and 0.030, respectively), and SUA ($p = 0.007$). Rheumatoid factor positivity and level were associated with thicker cIMT ($p = 0.042$ and 0.039, respectively). SUA maintained a significant correlation with cIMT in the multivariate analysis together with age, low-density lipoprotein, and triglyceride level. The model explained 55% (R2 55) of the causes of thick cIMT among RA population. SUA seems to be a cardiovascular risk factor in RA, as manifested by increase in the cIMT.

Keywords Atherosclerosis · Cardiovascular disease · Carotid intima-media thickness · Rheumatoid arthritis · Serum uric acid · Ultrasound

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Introduction

Overall world prevalence of rheumatoid arthritis (RA) range from 0.55 to 1%, which make it the most common chronic inflammatory condition [1, 2] that associated with many hormones and metabolic peptides [3]. Among RA mortality risk is 1.5 higher than general population and occurs largely as a result of higher rates of cardiovascular disease (CVD) [4]. A recent meta-analysis shows that standardized mortality ration (SMR) ranges from 0.99 to 3.82 for myocardial infarction and from 1.08 to 2 for cerebrovascular diseases in RA [5].

Cardiovascular and cerebrovascular diseases are strictly related to an accelerated atherosclerotic process. This accelerated atherosclerosis cannot fully explain by several traditional CV risk factors [6]. Serum uric acid (SUA) has been suggested as a potent CV risk factor in early onset RA, and it is related to the traditional CV risk factors [7]. Elevated SUA is often accompanied by obesity, hypertension [8], hyperlipidemia [9], glucose intolerance [10], renal disease [11], and CV risk factors

clustering [12], all of which play a causal role in the pathogenesis of CVD. Therefore, SUA may contribute to atherosclerosis through several pathways including deleterious effects on endothelial dysfunction, oxidative metabolism, platelet adhesiveness, hemorheology, and platelet aggregation [13, 14].

Ultrasound (US)-measured carotid intima-media thickness (cIMT) is a well-validated surrogate measure of the risk of coronary and cerebrovascular disease [15–17]. Higher cIMT has been shown to predict future ischemic cardiac and cerebral events among asymptomatic people [16–18]. In several prospective follow-up studies, cIMT has been used as an outcome variable to study determinants of progression vessel wall abnormalities [19–21].

Whether SUA is merely a marker that reflects the integration of comorbidities and subclinical renal impairment or a true risk-causative factor for cardiovascular outcome remains as an important question. Moreover, among RA patients, the role of hyperuricemia has not been well studied and only a few papers have addressed this issue [22, 23]. Given the excess burden of CVD in patients with RA and the potential role of SUA as a CV risk factor, this cross-sectional observational study aimed to examine the relation of SUA with CVD in RA population. We investigated subclinical atherosclerosis by measuring cIMT non-invasively by US.

Patients and methods

Fifty-three patients who fulfilled the American College of Rheumatology 1987 criteria for classification of RA [24] were included. We excluded patients with diabetes, hypertension, gout, renal disease, pregnant women, patients on diuretics medications, and those with history of CVD and/or cerebrovascular disease. The study protocol was approved by the ethical approval committee of the Ministry of Health and Prevention of United Arab Emirates, and written informed consent was obtained from all patients. Past medical history was obtained by reviewing doctors' chart including age, smoking status (current/past smoking and number of cigarettes per day) and duration of smoking, RA duration, age at RA symptoms onset, presence of rheumatoid factor (RF), rheumatoid level (NR 0.0–14 IU/ml), current medications, comorbidities (i.e., hypertension, dyslipidemia, diabetes, gout, and renal diseases) and family history of RA, CVD, and cerebrovascular diseases were recorded. Family history of premature CV events was defined as myocardial infarction or ischemic stroke occurred in a first degree relative before the age of 55 years in males or before the age of 65 years in females. Gout was defined as either use of hypourecamic agents or clinical diagnosis. Hypertension was defined as recorded blood pressure ≥ 140/90 or use of antihypertensive medications.

The patients underwent detailed physical examination and laboratory investigations within few days (±3 days) before cIMT US measurement. They were examined for joints tenderness and swelling, and the disease activity score for 28 joints (DAS 28) was calculated using erythrocyte sedimentation rate (ESR; NR 0.0–30 mm/h) and C-reactive protein rate (CRP; 0.0–5.0 mg/). Standing height and weight were measured. Blood pressure (systolic (SBP) and diastolic blood pressure (DBP)) measured in the right upper arm of patients in a seated position using an automatic oscillometric blood pressure recorder. Body mass index (BMI) was calculated using the formula of weight in kilograms divided by height in meters. A fasting blood sample was obtained for measurement of SUA (NR 155–476 μmole/l), plasma glucose (NR 4.6–6.4 mmole/l), total cholesterol (NR 2.0–2.5 mmole/l), high-density lipoprotein (HDL; NR 1.0–1.6 mmole/l), low-density lipoprotein (LDL; NR 0.0–2.5 mmole/l), triglycerides (TG; NR 0.4–1.9 mmole/l), urea (NR 0.0–8.3 mmole/l), and creatinine (NR 44–133 μmole/l).

cIMT US assessment

cIMT US measures were obtained using a real-time US scanner, equipped with a 7.5 MHz linear probe by a single sonographer. Patients were placed in supine position, with the head turned away from the sonographer, and the neck extended with mild rotation. The cIMT was taken as the distance between the intima-luminal interface and the media-adventitial interface, being cIMT measured in the far wall of both carotid arteries, about 10 mm proximal to the bifurcation of the carotid artery (bulb). Three images were obtained for each side, and the average of the six measured were used for analysis.

Statistical analysis

Summary statistical analysis results of baseline characteristics are expressed as percentages for categorical data and mean ± SD for continuous variables. cIMT was logarithmically transformed. The correlation between cIMT and other variables were calculated using simple linear-regression analysis with cIMT as a dependent variable. Covariates were SUA level, traditional cardiovascular risk factors, and inflammatory markers. Statistical significance was accepted as p value < 0.05. Multivariate model included all the variables that were significantly related to the cIMT in the univariate models.

Results

Fifty-three patients were included in the study. Table 1 shows demographics and RA characteristics. The mean age of the participants was 48 ± 14 years, with 5 males (age 57 ± 18.5) and 48 females (age 47 ± 13.6). The mean age for RA

Table 1 Demographic details, RA characteristics, and laboratory values of RA patients

Demographic details	
Male:female	5:48
Mean age (SD, year)	48 (14)
Male mean age (SD, year)	57 (18.5)
Female mean age (SD, year)	47 (13.6)
Body mass index (SD, kg/m^2)	28 (7)
Rheumatoid arthritis characteristics	
Disease duration, mean (SD, months)	6.8 (9.4)
Age at RA symptoms onset	41 (14)
Age at RA diagnosis	42 (15)
Tender joint count (of 28)	14 (11)
Swollen joint count (of 28)	3 (5)
Morning stiffness duration (minutes)	82 (216)
Rheumatoid factor level	54 (108)
Disease activity score (DAS) 3v-ESR	5.2 (1.4)
Disease activity score (DAS) 3v-CRP	4.5 (1.4)
Rheumatoid factor positive, *n* (%)	41 (77%)
Laboratory values	
Uric acid level	249 (82)
ESR (mm/h)	55 (47)
CRP (mg/l, normal <6)	24 (30)
Hemoglobin (gm/dl)	12 (1.5)
Cholesterol (mmol/l)	4.6 (1.0)
Triglyceride (mmol/l)	1.3 (0.7)
HDL level (mmol/l)	1.3 (0.4)
LDL cholesterol (mmol/l)	2.7 (0.9)
Cardiovascular risk factors	
Body mass index (kg/m^2)	28 (7.0)
Smoking, ever, *n* (%)	5.0 (9.4)
Family history of CVD, *n* (%)	3.0 (5.7)
Systolic blood pressure	128 (18)
Diastolic blood pressure	76 (11)

RA rheumatoid arthritis, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *CVD* cardiovascular disease, *n* number, *SD* standard deviation

symptoms onset was 41 ± 14 years. At the study time, the mean RA duration was 6.8 ± 9.4 years with forty-one (77%) were RF positive with RF level of 54 ± 108 IU/ml (NR 0.0–14 IU/ml) using immunotubidimetric technique. CV risk factors analysis showed a mean BMI of 28 ± 7 kg/m^2, SBP 128 ± 18 mmHg, and DBP 76 ± 11 mmHg. History of smoking ever in 5 (9.4%) patients and 3 (5.7%) patients had a family history of CVD.

Univariate analysis showed a positive linear relationship between cIMT and age of the patients ($p < 0.001$), SUA ($p = 0.007$), age at RA symptoms onset ($p = 0.010$), age at RA diagnosis ($p = 0.003$), number of cigarettes consumed per day ($p < 0.001$) (with mean cIMT for those who consumed less than 20 cigarette per day was 0.53 vs. 0.87 mm for 20 cigarettes or more), SBP ($p = 0.005$), and DBP ($p = 0.030$) (Table 2).

RA patients with positive RF had thicker cIMT than patients with negative RF (mean cIMT 0.596 vs. 0.525 mm, respectively, $p = 0.042$). The level of RF similarly showed a positive correlation with cIMT ($p = 0.039$), and those who had rheumatoid nodules showed thicker cIMT compared to negative rheumatoid nodules patients (0.653 vs. 0.558 mm, respectively, $p = 0.027$).

Adjusting for confounding variables by including all the variables that showed a significant correlation with the cIMT in the univariate analysis, SUA maintained a significant correlation with cIMT in the multivariate analysis as an independent factor in determining the thickness of cIMT. Other independent factors that maintained the significant linear relation to cIMT were age, LDL, and TG. The model explained 55% (R2 55) of the causes of thick cIMT among our RA population.

Discussion

This study showed a positive association between SUA and cIMT in RA population. The presence of uric acid in the atherosclerotic plaque has been postulated to play a role in the development of atherosclerosis [25], and this might explain the positive linear relationship that exists between the SUA and the cIMT among our RA patients.

Although previous studies have shown that SUA is associated with many risk factors for coronary artery disease, such as hypertension, hyperlipidemia, diabetes mellitus, and obesity [10, 26, 27], these traditional CV risk factors were not increased among our RA sample. Therefore, the positive correlation between SUA and cIMT might be due to other mechanism other than traditional CV factors.

We reported earlier a strong correlation exist between endothelial dysfunction and cIMT progression in RA [28]. Uric acid promotes endothelial dysfunction [29] by decreasing nitrous oxide bioavailability and increasing oxidative stress [30]. It also increases platelet activation, up-regulate the expression of platelet derived growth factor and monocyte chemo-attractant protein-1 [31, 32], increase platelet adhesiveness [13, 33], and stimulate vascular smooth muscle proliferation. Additionally, uric acid has also been associated with increased inflammatory markers such as CRP [34] which have been implicated in peripheral vascular disease [35]. Such effects may interact synergistically with the high degree of systemic inflammation in RA to promote increased atherogenesis, which can be expressed as an increase in the cIMT.

Among our sample, we found that older age at RA onset and arterial hypertension were significantly associated with cIMT. This is in consistence with Jacobsson et al. who identified that among factors associated with excess, CV mortality in RA patients were male genders, older age at RA onset, and

Table 2 Univariate and multivariate linear-regression analysis of the relationship between cIMT, selected RA features, CV risk factors, and uric acid in 53 patients with established RA

Variables	R^2	Standardized β coefficient	SE	*t*	*p*	CI
Univariate model						
Age	0.42	0.009	0.001	6.04	0.000	0.006, 0.012
Age at RA onset	0.13	0.005	0.001	2.69	0.010	0.001, 0.009
Age at RA diagnosis	0.16	0.005	0.002	3.10	0.003	0.002, 0.009
Male gender[a]	0.07				0.062	
History of smoking, ever[a]	0.06				0.068	
Number of consumed cigarette/day[a]	0.26				0.000	
Systolic blood pressure	0.15	0.004	0.001	2.95	0.005	0.001, 0.007
Diastolic blood pressure	0.09	0.005	0.002	2.24	0.030	0.001, 0.010
Body mass index	0.00	0.000	0.004	0.06	0.95	0.008, 0.009
Number of swollen joints (28)	0.04	0.009	0.006	1.53	0.132	0.002, 0.027
Number of tender joints (28)	0.01	0.002	0.003	0.71	0.479	−0.003, 0.007
DAS-28 (ESR)	0.01	0.011	0.018	0.61	0.545	0.026, 0.049
DAS-28 (CRP)	0.00	0.000	0.020	0.01	0.989	0.039, 0.041
RA nodules presence[a]	0.09				0.027	
RF presence[a]	0.08				0.042	
RF level	0.09	0.001	0.002	2.12	0.039	0.000, 0.001
LDL	0.03	0.039	0.031	1.26	0.212	−0.021, 0.012
HDL	0.03	−0.075	0.062	−1.20	0.237	−0.201, 0.051
Cholesterol	0.01	0.020	0.027	0.74	0.460	−0.034, 0.075
Triglyceride	0.01	−0.027	0.040	−0.67	0.504	−0.110, 0.055
SUA	0.13	0.001	0.000	2.81	0.007	0.000, 0.001
Multivariate model						
Age		0.008	0.002	5.15	0.000	0.005, 0.011
LDL		0.067	0.023	2.84	0.007	0.019, 0.011
TG		0.067	0.031	2.20	0.033	0.006, 0.129
Uric acid		0.001	0.000	2.49	0.017	0.000, 0.001

Each parameter included in the univariate linear-regression analysis. Adjusted R^2 of the multivariate linear-regression model = 0.55. The underlined numbers are the significant *p* value of <0.05

aANOVA test

DAS-28 (*ESR*) disease activity score-28 (erythrocyte sedimentation rate), *DAS-28* (*CRP*) disease activity score-28 (C-reactive protein), *RA* rheumatoid arthritis, *RF* rheumatoid factor, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *SUA* serum uric acid, *TG* triglyceride.

arterial hypertension [36]. The effect of age on the cIMT thickness had been explored in a study previously published by our group, which showed a strong correlation between age of early RA patients and cIMT. The slope of the univariate regression line and age was steeper in RA patients than controls, suggesting more rapid progression of cIMT thickness in RA patients than their age and sex matched controls. In the same study, we reported a correlation between high blood pressure and cIMT among early RA [37].

To assess the CV risk in RA patients, the risk equation has to be multiplied by 1.5 when two of the following criteria are met: disease duration longer than 10 years, presence of RF or anti-cyclic citrullinated peptide (CCP) antibodies, and extra-articular manifestation [38]. Our study found that two out of the three criteria (disease duration and presence of RF) were associated with cIMT, which support the association of longer and greater RA activity with increased risk of CVD. In addition to RF positivity, RF level seems to play an important role in the atherosclerosis progression in RA as RF titer has been found to be the major risk factor for increased cIMT in RA patients [39].

Dyslipidemia is an important risk factor for CVD. After adjustment for the traditional CV risk factors and inflammatory markers, our study found that both LDL and TG level showed a significant positive relationship with cIMT. Hyperlipidemia is one of several dyslipidemic patterns and is considered a major modifiable risk factor [40]. Particularly, hypertriglyceridemia has been shown to be correlated to cIMT in RA and to contribute to oxidative injury of the vascular wall [41].

Our study provides statistical evidence that elevated SUA is likely to impact on CVD. Biological evidence also supports our findings, highlighting the role of SUA in the pathogenesis of endothelial injury [42]. This finding raises the question of whether pharmaceutical reduction of SUA, with urate-lowering therapy such as allopurinol, can reduce CVD risk.

A major shortcoming of our study is that serum uric acid was done as a single measurement. Furthermore, it is applied to United Arab Emirates population only and not pertains to other ethnical groups. This study is strengthened by our ability to correct for confounding traditional and non-traditional cardiovascular risk factors.

Adjusting for confounding variables by including all the variables that showed a significant correlation with the cIMT in the univariate analysis, SUA maintained a significant correlation with cIMT in the multivariate analysis as an independent factor in determining the thickness of cIMT.

In conclusion, SUA was significantly associated with increased cIMT, an independent marker of atherosclerosis and CVD. In RA, SUA may interact synergistically with the high degree of systemic inflammation to promote increased atherogenesis. Prospective studies are necessary to understand the effect of SUA on cIMT in RA patients and to address whether the control of SUA level as modifiable CV risk factor can improve CVD related outcome.

cIMT, carotid intima-media thickness; CVD, cardiovascular disease; RA, rheumatoid arthritis; RF, rheumatoid factor

Compliance with ethical standards

Disclosures None.

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