Prognostic role of coronary calcification in patients with rheumatoid arthritis and systemic lupus erythematosus

K.-H. Yiu[1], M-Y. Mok[2], S. Wang[3], G.-C. Ooi[3], P.-L. Khong[3], C.-S. Lau[2], H.-F. Tse[1,4]

[1]Cardiology Division, Department of Medicine; [2]Division of Rheumatology, Department of Medicine; [3]Department of Diagnostic Radiology; [4]Research Centre of Heart, Brain, Hormone and Healthy Aging, Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong.

Abstract

Objectives

To study the predictive value of coronary calcification score (CCS) for future cardiovascular (CVS) events as detected by multi-detector computed tomography (MDCT) in patients with rheumatoid arthritis(RA) and systemic lupus erythematosus (SLE).

Methods

A total of 152 patients with RA and SLE, and 106 healthy controls underwent MDCT to measure CCS. All patients were prospectively followed up for major CVS events.

Results

Compared with controls, patients with RA and SLE had a significantly higher mean CCS (42.2±154.3 vs. 1.4±13.0, p<0.01) and prevalence of CCS 1–10, CCS 11–100 and CCS>100 (all p<0.05). After a mean period of 4.3±0.6 years, major CVS events occurred in 10 patients with RA and SLE. In patients with RA and SLE, a higher major CVS events rate occurred in patients with CCS 1–10 (5.0%), CCS 11–100 (14.3%) and CCS >100 (40.0%) than those with CCS=0 (1.0%, p<0.01). Multivariate Cox regression analysis revealed that hypercholesterolemia (hazard ratio (HR) 11.2, confidence interval (CI 1.4–89.3, p=0.02) and CCS>100 (HR 11.1, CI 1.31–95.0, p=0.03) were independent predictors of combined events.

Conclusion

Coronary calcification detected by MDCT independently predicts CVS events in patients with RA and SLE. Risk stratification by assessment of CCS may have an important role in patients with systemic inflammatory disease.

Key words

coronary calcification, rheumatoid arthritis, systemic lupus erythematosus, cardiovascular, computed tomography

Kai-Hang Yiu, MBBS
Mo-Yin Mok, MBBS
Silun Wang, MD
Gaik-Cheng Ooi, MD
Pek-Lan Khong, MD
Chak-Sing Lau, MD
Hung-Fat Tse, MD, PhD

Please address correspondence to:
Hung-Fat Tse, MD, PhD,
Cardiology Division,
Department of Medicine,
University of Hong Kong,
Rm 1928, Block K,
Queen Mary Hospital, Hong Kong.
E-mail: hftse@hkucc.hku.hk

Received on April 23, 2011; accepted in revised form on October 25, 2011.

Competing interests: none declared.

Introduction

Systemic inflammatory diseases including rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) are associated with increased mortality, mainly caused by cardiovascular (CVS) disease (1-4). The increased CVS events observed in RA and SLE cannot be fully explained by traditional risk factors which suggested that chronic inflammation and genetic factors may contribute to the development of premature atherosclerosis (1, 5-8). Indeed, several lines of evidence supported the notion that chronic inflammation in genetically predisposed individuals played a pivotal role in the development of various stages of atherosclerosis (5, 6, 9-11).

In view of the elevated CVS risk in patients with RA and SLE, surrogate markers to detect premature atherosclerosis may identify high risk subjects for early preventive measures as well as predict future events. The advent of multi-detector computed tomography (MDCT) allows noninvasive detection of the extent and severity of atherosclerosis in vascular beds by imaging arterial calcification to reflect the presence of calcified atherosclerotic plaque. In general population, coronary calcification has been proven to be a powerful predictor for future CVS events (12). Studies by our group (13, 14) and others (15, 16) have previously shown that patients with RA and SLE had an increased prevalence and extent of coronary calcification. However, the predictive role for future CVS events by using coronary calcification in patients with RA and SLE has not been explored.

Therefore the aim of the present study is to evaluate the role of coronary calcification detected by MDCT in prediction of future CVS events in patients with RA and SLE.

Methods

Study population

From January 2006 to January 2007, 154 consecutive Chinese patients age >18 years old who met the diagnostic criteria for RA (17) and SLE (18) were prospectively enrolled. Furthermore, 106 age- and sex-matched controls who did not meet the classification criteria for any inflammatory disease were also recruited as control from a local health check programme. None of the study subjects had a documented history of cardiovascular diseases including stroke, myocardial infarction, peripheral vascular disease and angina. The study was approved by the institutional ethical review board and all subjects gave their written informed consent.

Study protocols

Data on baseline demographic, clinical characteristics and blood sampling were obtained prospectively in the same day from the study subjects. CVS risk factors, including history of smoking, diabetes, hypercholesterolemia, and hypertension were assessed. The body height and weight, blood pressure and body mass index of all subjects were measured as previously described (19). Hypertension was defined as either resting systolic or diastolic blood pressure ≥140/90 mmHg at two different times or on medications. Diabetes was defined as a serum fasting glucose of ≥7.1 mmol/L or on oral hypoglycaemic agent. Hypercholesterolemia was defined as a fasting total serum cholesterol level of ≥4.9 mmol/L or on medications. Smoking status was recorded as either smoker (past and current) or nonsmoker. For patients with RA, duration of disease, presence of rheumatoid factor and current use of medication were recorded. Similarly, demographic data including duration of disease, anti-double stranded DNA antibodies (anti-dsDNA) and current use of medications in patients with SLE were retrieved.

Fasting blood samples were obtained from all subjects to determine serum creatinine, glucose and lipid levels. C-reactive protein level was measured by using a Hitachi 747 analyzer (Boehringer Mannheim, Mannheim, Germany), and a particle-enhanced immunoturbidimetric assay (Roche Diagnostics, Mannheim, Germany) as described previously (19).

Multi-detector computed tomography imaging

All subjects underwent computed tomography imaging of coronary arteries using a 64 slices MDCT (Lightspeed,

VCT, GE Healthcare, USA). Details of MDCT imaging were previously described (14, 20). In brief, all scans were performed with the subjects in the supine position which included regions from the arch of the aorta to the fundus of the heart. Prospective electrocardiogram-gated cardiac scan was obtained with following scan parameters: rotation time=0.35s; slice thickness=2.5mm; 120kV; 250 mA; trigger delay=70% R-R interval. Patients were instructed to hold their breath for 30s during scanning.

The acquired MDCT images were reviewed at the post-processing image workstation (Advantage windows 4.02, GE Healthcare, USA). Complete data were available from all the scans, without misregistration of slices due to artifacts of motion, respiration, or asynchronous electrocardiographic triggering. To ensure the continuity and consistency of the interpretation of calcium scores (CS), two expert investigators (S.W., G.C.O), who were unaware of the subjects' clinical status analysed all the scans. The interobserver and intraobserver variability correlation coefficients of CCS measurements were 0.92 and 0.91, respectively.

Analysis of coronary calcification by multi-detector computed tomography

Measurement of coronary calcification score (CCS) was performed by a commercially available software "smart score" (General Electric Healthcare, USA) using the threshold option set for pixels greater than 130 Hounsfield units and expressed in Agaston unit. Patient's CCS was calculated as sum of calcium score in left main coronary artery, left anterior descending artery, left circumflex coronary artery, right coronary artery and posterior descending artery. Patients were further stratified into 4 groups according to their range of CCS: CCS=0, CCS=1–10, CCS=11–100 and CCS>100.

Follow-up

All patients with RA and SLE were followed up for a minimum of 3 years after CCS assessment in the outpatient clinic, and no patients lost follow-up during the study period. Outcome of controls subjects were retrieved by the inter-hospital computer system or through telephone interviews. Major CVS events were a composite endpoint of stroke, non-fatal myocardial infarction (MI), and CVS mortality. The definition of MI was based on the presence of typical chest pain, elevated cardiac enzyme levels, and typical electrocardiogram changes (21).

Statistical analysis

Continuous variables are expressed as mean ± standard deviation and compared using either Student's *t*-test or Wilcoxon's rank-sum test as appropriate. Categorical variables were reported as frequencies and compared using the chi-square or the Fisher exact test if at least one cell had an expected cell count below 5. Kaplan-Meier curve was constructed and the outcomes of different CCS groups were compared using the log-rank test. One-way analysis of variance (ANOVA) was used to examine the differences in clinical characteristic among different CCS groups. A multivariable Cox regression model and stepwise elimination approach were used to determine the independent predictors of major CVS events. Factors such as age, cardiovascular risk factors including hypertension, diabetes mellitus, hypercholesterolemia, current smoking history and CCS were entered into the model. All statistical analyses were performed using the statistical package SPSS for windows (Version 15.0, SPSS, Chicago, USA). A *p*-value <0.05 was considered to be statistically significant.

Results

Clinical characteristics

The mean age of the overall study population was 49.2±11.2, 83.1% were female and the duration of disease was 12.6 years. Baseline characteristics of patients with RA and SLE and controls are presented in Table I. Patients with RA and SLE were more likely to have a history of hypertension and a higher fasting glucose level while controls had a higher body mass index, prevalence of hypercholesterolemia and serum levels of high-density and low-density lipoprotein level. Furthermore, the mean age, systolic blood pressure and serum levels of total cholesterol, low-density lipoprotein, fasting glucose and C-reactive protein in patients with RA were significantly higher than those in patients with SLE.

Among those patients with RA, 61 (72%) of them had a positive rheumatoid factor and 66 (78%) received active treatment for RA, including corticosteroid (n=13, 15%), and methotrexate (n=57, 67%).

In patients with SLE, their mean anti-ds DNA level was 22.5±38.5 IU/ml. Among them, 60 (87%) received active treatment for SLE including hydroxycholoroquine (n=40, 58%), corticosteroid (n=22, 61%), azathioprine (n=38, 55%), cyclophosphamide (n=6, 9%) and mycophenonate mofetile (n=19, 28%).

Prevalence and extent of coronary calcification

The mean CCS of patients with RA and SLE was significantly higher compared with controls (42.2±154.3 *vs*. 1.4±13.0, $p<0.01$). Furthermore, patients with RA and SLE had a higher prevalence of CCS 1–10 (13.0 *vs*. 4.7%, $p=0.03$), CCS 10–100 (9.1 *vs*. 0.9%, $p<0.01$) and CCS >100 (9.7 *vs*. 0.9%, $p<0.01$) compared with controls (Fig. 1).

Clinical characteristic among different CCS groups is shown in Table II. A significant trend of older age, higher systolic blood pressure, history of hypertension and increased in creatinine level were noted in patients with higher CCS group.

Clinical outcomes

During a mean follow-up period of 4.3±0.6 (25^{th}–75^{th} quartile range=4.2–4.6) years, a total of 10 major CVS events (stroke=5, non-fatal MI=2, CVS mortality=3) occurred in patients with RA and SLE *versus* none occurred in controls ($p<0.01$). The annualised major CVS event rates in patients with RA and SLE was 1.5%, and no difference was noted between patients with RA and SLE (1.7% *vs*. 1.4%, $p=1.0$).

In patients with RA and SLE, a higher major CVS events rate occurred in patients with CCS 1–10 (5.0%), CCS 11–100 (14.3%) and CCS >100 (40.0%) than those with CCS=0 (1.0%, $p<0.01$).

Table I. Clinical characteristics in controls, patients with rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE).

	Controls n=106	RA/SLE n=154	*p*-value	RA n=85	SLE n=69	*p*-value
Age (years)	50.5 ± 8.2	48.2 ± 12.9	0.08	53.9 ± 11.8	41.3 ± 10.6	<0.01
Female (%)	83 (78.3)	133 (86.4)	0.10	73 (85.9)	60 (87)	1.00
Systolic blood pressure (mmHg)	119.3 ± 13.2	122.8 ± 18.0	0.08	126.9 ± 18.4	117.7 ± 16.1	<0.01
Diastolic blood pressure (mmHg)	73.0 ± 9.5	75.2 ± 9.6	0.07	75.7 ± 10.6	74.7 ± 8.3	0.48
Body-mass index (kg/m^2)	23.8 ± 3.4	22.0 ± 3.6	<0.01	22.1 ± 3.6	21.9 ± 3.7	0.74
Smoker (%)	9 (8.5)	19 (12.3)	0.42	9 (10.6)	10 (14.5)	0.47
Hypertension (%)	9 (8.5)	31 (20.1)	0.01	20 (23.5)	11 (15.9)	0.31
Diabetes (%)	0 (0)	5 (3.2)	0.08	3 (3.5)	2 (2.9)	1.00
Hypercholesterolemia (%)	27 (25.5)	7 (4.5)	<0.01	3 (3.5)	4 (5.8)	0.70
Total cholesterol (mmol/L)	5.1 ± 7.4	4.8 ± 1.1	0.01	5.0 ± 1.1	4.4 ± 1.0	<0.01
Triglycerides (mmol/L)	1.3 ± 0.8	1.3 ± 0.6	0.81	1.3 ± 0.6	1.2 ± 0.6	0.60
High-density lipoprotein (mmol/L)	1.6 ± 0.4	1.5 ± 0.4	0.03	1.5 ± 0.4	1.5 ± 0.5	0.49
Low-density lipoprotein (mmol/L)	2.9 ± 0.7	2.7 ± 0.9	0.03	2.9 ± 0.8	2.4 ± 0.8	<0.01
Urea (mmol/L)	4.9 ± 1.0	5.4 ± 4.5	0.23	5.2 ± 1.8	5.7 ± 0.7	0.62
Creatinine (μmol/L)	66.9 ± 13.6	68.7 ± 20.2	0.46	69.6 ± 20.3	67.2 ± 20.0	0.51
Fasting glucose (mmol/L)	4.8 ± 0.4	5.8 ± 2.2	<0.01	6.3 ± 2.3	4.8 ± 1.8	<0.01
C-reactive protein (mg/dL)	–	0.8 ± 1.1	–	1.5 ± 1.4	0.6 ± 0.5	0.02
Duration of disease (years)	–	12.6 ± 9.5	–	12.6 ± 10.8	12.6 ± 7.8	0.97

Data are expressed as means (S.D.) for continuous variables and as a percentage for categorical variables.

The Kaplan-Meier survival curve comparing different CCS groups is shown in Figure 2. Overall CCS >0 was significantly predictive of combined events (log rank=31.8, $p<0.01$). Compared with patients with CCS=0, patients with CCS >100 was predictive of combined events (log rank=17.6, $p<0.01$). However, there were no significant differences in major CVS events between patients with CCS >100 *versus* those with CCS 11–100 ($p=0.18$) and CCS 1–10 ($p=0.73$).

Predictive value of coronary calcification

Cox proportional hazard models were used to evaluate the impact of CCS results on the occurrence of major CVS events (Table III). Univariate analysis showed that older age, history of hypertension, diabetes, hypercholesterolemia and CCS >100 were associated with increased major CVS events. Multivariate Cox regression analysis revealed that hypercholesterolemia (hazard ratio [HR] 11.2), confidence interval ([CI] 1.4–89.3, $p=0.02$) and CCS >100 (HR 11.1, CI 1.31–95.0, $p=0.03$) were independent predictors of combined events.

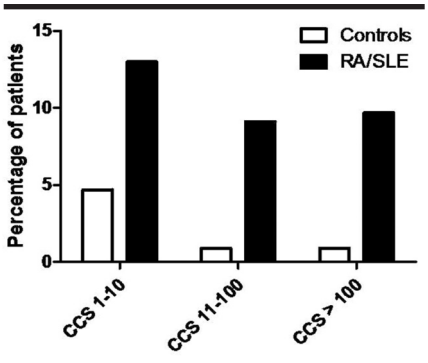

Fig. 1. Percentage of controls, rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) patients in different coronary calcification score (CCS) groups.

Discussion

The present study confirmed that patients with RA and SLE had a higher prevalence and extent of coronary calcification compared to age and sex-matched controls. More importantly, the current study is the first to demonstrate that the presence of coronary calcification detected by MDCT is associated with major CVS events in patients with RA and SLE. Moreover, the

Table II. Clinical Characteristics of patients with rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) stratified according to coronary calcium score (CCS) groups.

	CCS=0 n=105	CCS 1-10 n=20	CCS 11-100 n=14	CCS>100 n=15	*p*-value
Age (years)	43.3 ± 10.4	54.2 ± 11.3	57.1 ± 10.8	66.6 ± 6.5	<0.01
Female (%)	94 (89.5)	17 (85)	9 (64.3)	13 (86.7)	0.08
Systolic blood pressure (mmHg)	118.8 ± 16.0	125.7 ± 20.4	132.6 ± 17.2	137.2 ± 18.4	<0.01
Diastolic blood pressure (mmHg)	74.1 ± 9.5	77.0 ± 9.3	77.1 ± 9.8	79.4 ± 10.1	0.14
Body-mass index (kg/m^2)	21.8 ± 3.6	22.7 ± 3.4	23.3 ± 3.4	21.8 ± 3.6	0.38
Smoker (%)	12 (11.4)	3 (15.0)	3 (21.4)	1 (6.7)	0.63
Hypertension (%)	15 (14.3)	3 (15)	4 (28.6)	9 (60)	<0.01
Diabetes (%)	3 (2.9)	0 (0)	7 (7.1)	1 (6.7)	0.58
Hypercholesterolemia (%)	3 (2.9)	2 (10.0)	2 (14.3)	0 (0)	0.12
Total cholesterol (mmol/L)	4.6 ± 1.1	5.1 ± 0.7	4.9 ± 1.1	5.2 ± 1.4	0.12
Triglycerides (mmol/L)	1.2 ± 0.7	1.4 ± 0.7	1.3 ± 0.5	1.4 ± 0.6	0.39
High-density lipoprotein (mmol/L)	1.5 ± 0.5	1.4 ± 0.4	1.6 ± 0.4	1.6 ± 0.4	0.71
Low-density lipoprotein (mmol/L)	2.6 ± 0.9	2.9 ± 0.7	2.7 ± 0.8	3.0 ± 1.3	0.26
Urea (mmol/L)	5.0 ± 5.3	5.8 ± 1.8	6.0 ± 2.1	6.8 ± 1.8	0.47
Creatinine (μmol/L)	64.2 ± 16.3	70.2 ± 11.1	76.3 ± 20.0	87.9 ± 33.7	<0.01
Fasting glucose (mmol/L)	5.5 ± 2.0	5.8 ± 1.6	6.4 ± 3.8	6.8 ± 2.3	0.14
C-reactive protein (mg/dL)	1.1 ± 1.0	1.0 ± 1.2	1.2 ± 0.9	1.2 ± 1.0	0.82
Duration of disease (years)	12.0 ± 9.6	10.9 ± 8.3	14.4 ± 8.1	17.6 ± 11.0	0.12

Data are expressed as means (S.D.) for continuous variables and as a percentage for categorical variables.

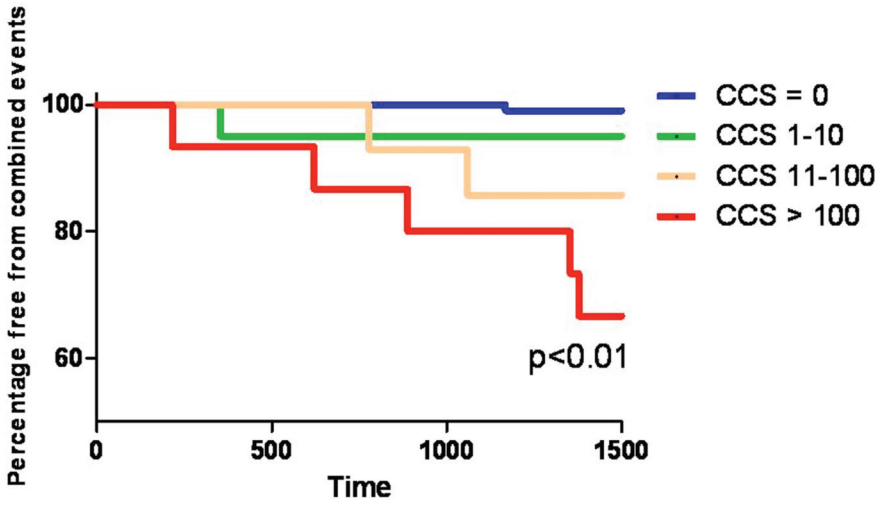

Fig. 2. Kaplan-Meier survival curves for combined events in patients with rheumatoid arthritis and systemic lupus erythematosus according to different coronary calcification score (CCS) groups.

Table III. Cox-regression model between coronary calcification score (CCS) >100 and combined events.

	Univariate			Multivariate		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age	1.13	1.05–1.21	<0.01			
Female gender	0.61	0.13–2.87	0.53			
Body-mass index	1.09	0.92–1.29	0.32			
Smoker	0.81	0.10–6.39	0.84			
Hypertension	4.2	1.22–14.5	0.02			
Diabetes	8.50	1.80–40.25	<0.01	3.22	0.57–18.19	0.19
Hypercholesterolemia	6.09	1.30–28.7	0.02	11.16	1.39–89.32	0.02
Duration of disease	1.01	0.96–1.08	0.66			
CCS > 100	16.5	4.65–58.58	<0.01	11.14	1.31–95.0	0.03

presence of CCS >100 predicted the occurrence of major CVS events over a period of 4.3 years independent to other risk factors.

It has been increasingly recognised that patients with RA and SLE died prematurely of CVS diseases which are independent of traditional risk factors. Surrogate markers for atherosclerosis including carotid intima-media thickness (IMT) (22, 23), brachial flow-mediated dilatation (24-26) and pulse wave velocity (27, 28) have been shown to be impaired in patients with RA and SLE. Indeed, a study also showed that subclinical atherosclerosis progressed in patients with RA with severe disease despite periodic treatment with anti-TNFα monoclonal antibody infliximab.(29) Moreover, patients with RA and SLE have been demonstrated to have a higher prevalence and extent of coronary calcification detected by MDCT compared to controls (14-16). While a higher atherosclerotic burden detected by MDCT is noted in patients with RA and SLE (14-16), the potential predictive value of CCS as detected by MDCT for future CVS events remains unclear. In the present study, we prospectively studied the predictive role of CCS detected by MDCT in a cohort of patients with RA and SLE. Similar to results observed in the general population, a higher relative risk of future CVS events occurred with increasing CCS in patients with RA and SLE. Moreover, presence of CCS >100 predicted future CVS events independent of conventional CVS risk factors, duration of disease and degree of systemic inflammation measured by C-reactive protein.

In a recent study involving 47 patients with RA, carotid IMT was shown to be predictive of development of CVS events over a 5 year follow-up period regardless of the baseline CVS risk factors (30). While IMT is a well validated surrogate marker for atherosclerosis with prognostic value for future CVS events, a lack of cut-off value limited its widespread use in clinical practice. In contrast, CCS measured by MDCT has less inter-observer and intra-observer variability, and a cut-off value of 100 has been associated with CVS events across different ethnicity groups (16). By using a similar cut-off value of CCS >100 in this study, a relative risk of 11-fold for major CVS events was observed in patients with RA and SLE even after adjusting with conventional risk factors, duration of disease and C-reactive protein level. The 6.4% events rate during the follow-up of 4.3 years in the present cohort of patients with RA and SLE was higher compared to a reported 2.4% events rate in asymptomatic women in a 5-year follow-up period from the report of Women's Ischemic Syndrome Evalulation and the St. James Women Take Heart Project (31). Nevertheless, future studies are needed to evaluate the potential differences in the predictive values for CVS events between various surrogate markers for atherosclerosis (32).

Limitations

First, the relatively low major CVS event rate (~1.5% per year) in this young cohort of RA and SLE patients preclude the evaluation of a confident cut-off value for CCS in predicting future CVS events. Second, the present protocol in evaluating CCS cannot detect non-calcified atherosclerosis and detailed computed tomography coronary angiography was not performed. A recent study in patients with suspected coronary artery disease has shown that the absence of coronary calcification cannot exclude obstructive coronary stenosis or the need for revascularisation (33). Nevertheless, none of the subjects in this study had symptomatic coronary artery disease. The presence of antiphospholipid antibodies which is associated with stroke was not checked in all patients with SLE. Therefore, this could represent a potential bias of the result. In patients with SLE, renal involvement with nephrotic syndrome,

pro-thrombotic state due to antiphospholipid antibodies and uptake of high-dose corticosteroids may also affect the cardiovascular manifestation. Therefore, the prognostic role of CCS in individual disease subgroup (RA and SLE) would require future studies with larger population. Future studies are also needed to evaluate the prognostic role of anti-TNF in relation to the CCS results as it may reduce cardiovascular complications in rheumatic patients. Finally, it remains important to realise that, despite the reduced radiation burden, the risk of radiation exposure associated with MDCT should not be disregarded, particularly in younger patients with rheumatic diseases.

Conclusion

The current study is the first to demonstrate the prognostic value of CCS detected by MDCT in patients with RA and SLE. The initial results indicated that CCS measured by MDCT is a clinically useful tool to improve risk stratification in patients with RA and SLE for early preventive measures, such as statin therapy to reduce CVS events in high risk patients.

References

1. SOLOMON DH, KARLSON EW, RIMM EB *et al*.: Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis. *Circulation* 2003; 107: 1303-7.
2. MARADIT-KREMERS H, NICOLA PJ, CROWSON CS, BALLMAN KV, GABRIEL SE: Cardiovascular death in rheumatoid arthritis: a population-based study. *Arthritis Rheum* 2005; 52: 722-32.
3. MANZI S, MEILAHN EN, RAIRIE JE *et al*.: Age-specific incidence rates of myocardial infarction and angina in women with systemic lupus erythematosus: comparison with the framingham study. *Am J Epidemiol* 1997; 145: 408-15.
4. HAK AE, KARLSON EW, FESKANICH D, STAMPFER MJ, OSTENBADER KH: Systemic lupus erythematosus and the risk of cardiovascular disease: Results from the nurses' health study. *Arthritis Rheum* 2009; 61: 1396-402.
5. FISCHER LM, SCHLIENGER RG, MATTER C, JICK H, MEIER CR: Effect of rheumatoid arthritis or systemic lupus erythematosus on the risk of First-Time acute myocardial infarction. *Am J Cardiol* 2004; 93: 198-200.
6. GONZALEZ-GAY MA, GONZALEZ-JUANATEY C, LOPEZ-DIAZ MJ *et al*.: HLA-DRB1 and persistent chronic inflammation contribute to cardiovascular events and cardiovascular mortality in patients with rheumatoid arthritis. *Arthritis Rheum* 2007 15; 57: 125-32.
7. DESSEIN PH, CHRISTIAN BF, WOODIWISS AJ, NORTON GR, SOLOMON A: Public healthcare attendance associates with enhanced conventional and non-conventional atherosclerotic cardiovascular disease risk burdens in established rheumatoid arthritis. *Clin Exp Rheumatol* 2010; 28: 230-7.
8. DORIA A: Atherosclerosis and lupus: what we know and what we should know. *J Rheumatol* 2009; 36: 2380-2.
9. RODRÍGUEZ-RODRÍGUEZ L, GONZÁLEZ-JUANATEY C, PALOMINO-MORALES R *et al*.: TNFA -308 (rs1800629) polymorphism is associated with a higher risk of cardiovascular disease in patients with rheumatoid arthritis. *Atherosclerosis* 2011; 216: 125-30.
10. GONZALEZ-GAY MA, LLORCA J, PALOMINO-MORALES R *et al*.: Influence of nitric oxide synthase gene polymorphisms on the risk of cardiovascular events in rheumatoid arthritis. *Clin Exp Rheumatol* 2009; 27: 116-9.
11. LIBBY P: Inflammation in atherosclerosis. *Nature* 2002; 420: 868-74.
12. DETRANO R, GUERCI AD, CARR JJ *et al*.: Coronary calcium as a predictor of coronary events in four racial or ethnic groups. *N Engl J Med* 2008; 358: 1336-45.
13. WANG S, YIU KH, MOK MY *et al*.: Prevalence and extent of calcification over aorta, coronary and carotid arteries in patients with rheumatoid arthritis. *J Intern Med* 2009; 266: 445-52.
14. YIU KH, WANG S, MOK MY *et al*.: Pattern of arterial calcification in patients with systemic lupus erythematosus. *J Rheumatol* 9 A.D.; 36: 2212-7.
15. CHUNG CP, OESER A, RAGGI P *et al*.: Increased coronary-artery atherosclerosis in rheumatoid arthritis: relationship to disease duration and cardiovascular risk factors. *Arthritis Rheum* 2005; 52: 3045-53.
16. ASANUMA Y, OESER A, SHINTANI AK *et al*.: Premature coronary-artery atherosclerosis in systemic lupus erythematosus. *N Engl J Med* 2003; 349: 2407-15.
17. ARNETT FC, EDWORTHY SM, BLOCH DA *et al*.: The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988; 31: 315-24.
18. TAN EM, COHEN AS, FRIES JF *et al*.: The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982; 25: 1271-7.
19. CHAN YH, LAU KK, YIU KH *et al*.: Reduction of C-reactive protein with isoflavone supplement reverses endothelial dysfunction in patients with ischaemic stroke. *Eur Heart J* 2008; 29: 2800-7.
20. YIU KH, WANG S, MOK MY *et al*.: Role of circulating endothelial progenitor cells in patients with rheumatoid arthritis with coronary calcification. *J Rheumatol* 2010; 37: 529-35.
21. ALPERT JS, THYGESEN K, ANTMAN E, BASSAND JP: Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology committee for the redefinition of myocardial infarction: The Joint European Society of Cardiology/ American College of Cardiology Committee. *J Am Coll Cardiol* 2000; 36: 959-69.
22. VAN SIJL AM, PETERS MJ, KNOL DK *et al*.: Carotid intima media thickness in rheumatoid arthritis as compared to control subjects: a meta-analysis. *Semin Arthritis Rheum* 2011; 40: 389-97.
23. ROMAN MJ, SHANKER BA, DAVIS A *et al*.: Prevalence and correlates of accelerated atherosclerosis in systemic lupus erythematosus. *N Engl J Med* 2003; 349: 2399-406.
24. VAUDO G, MARCHESI S, GERLI R, PASSAUER J: Endothelial dysfunction in young patients with rheumatoid arthritis and low disease activity. *Ann Rheum Dis* 2004; 63: 31-5.
25. EL-MAGADMI M, BODILL H, AHMAD Y *et al*.: Systemic lupus erythematosus: an independent risk factor for endothelial dysfunction in women. *Circulation* 2004; 110: 399-404.
26. GONZALEZ-JUANATEY C, TESTA A, GARCIA-CASTELO A *et al*.: HLA-DRB1 status affects endothelial function in treated patients with rheumatoid arthritis. *Am J Med* 2003; 114: 647-52.
27. MAKI-PETAJA KM, HALL FC, BOOTH AD *et al*.: Rheumatoid arthritis is associated with increased aortic pulse-wave velocity, which is reduced by anti-tumor necrosis factor-therapy. *Circulation* 2006; 114: 1185-92.
28. SELZER F, SUTTON-TYRRELL K, FITZGERALD S, TRACY R, KULLER L, MANZI S: Vascular stiffness in women with systemic lupus erythematosus. *Hypertension* 2001;37:1075-82.
29. GONZALEZ-JUANATEY C, LLORCA J, GARCIA-PORRUA C *et al*.: Effect of anti-tumor necrosis factor alpha therapy on the progression of subclinical atherosclerosis in severe rheumatoid arthritis. *Arthritis Rheum* 2006; 55: 150-3.
30. GONZALEZ-JUANATEY C, LLORCA J, MARTIN J, GONZALEZ-GAY MA: Carotid intima-media thickness predicts the development of cardiovascular events in patients with rheumatoid arthritis. *Semin Arthritis Rheum* 2009; 38: 366-71.
31. GULATI M, COOPER-DEHOFF RM, MCCLURE C *et al*.: Adverse cardiovascular outcomes in women with nonobstructive coronary artery disease: a report from the Women's Ischemia Syndrome Evaluation Study and the St James Women Take Heart Project. *Arch Intern Med* 2009; 169: 843-50.
32. YIU KH, LAU KK, LAU CP, TSE HF: A review of surrogate markers for atherosclerosis: flow mediated dilatation; carotid intima media thickness; pulse wave velocity; ankle brachial index. *Vasc Dis Prev* 2008; 5: 234-45.
33. GOTTLIEB I, MILLER JM, ARBAB-ZADEH A *et al*.: The absence of coronary calcification does not exclude obstructive coronary artery disease or the need for revascularization in patients referred for conventional coronary angiography. *J Am Coll Cardiol* 2010; 55: 627-34.