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RESEARCH ARTICLE

Evaluation of Cardiovascular risk in Egyptian rheumatoid arthritis patients using carotid ultrasound and Coronary Artery Calcification Score to detect subclinical atherosclerosis.

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Abstract

Objective To assess the presence of subclinical atherosclerosis in patients with rheumatoid arthritis (RA) without clinically evident atherosclerosis or its complications and to determine the ability of Coronary Artery Calcification Score (CACS) and carotid ultrasonography in detecting subclinical atherosclerosis in rheumatoid arthritis (RA).

Methods A Case control study which included 100 patients with RA having disease duration more than 5 years and 50 healthy age and sex and BMI matched controls. Cases and controls symptomatic for atherosclerosis or having traditional risk factors for atherosclerosis were excluded. Both cases and controls were subjected to carotid ultrasound and CT imaging of coronary arteries. CV risk was calculated according to the Framingham risk score.

Results: CIMT in RA patients was significantly greater than that in controls (0.87 ± 0.09 mm mm versus 0.58±0.14 mm; mm; P < 0.001). RA patients was significantly greater in the presence of carotid plaque and coronary artery calcifications than that in controls . RA patients had higher Framingham risk score than control . CV risk was categorized in the RA patients according to the Framingham risk score mild (64*%), moderate and high risk(36%)*

Conclusions: Patients with RA exhibit premature atherosclerosis by way of increased CIMT and carotid plaques when compared to age and sex matched controls . RA patients had higher Framingham risk score than control.

Introduction

Reports of a number of studies have suggested that there is increased cardiovascular disease and mortality among patients with rheumatoid arthritis (RA) [1–5]. As a potential underlying mechanism for this observation, studies recently shown that active, untreated RA is associated with an adverse lipid profile that is conventionally accepted as a risk factor for cardiovascular disease [6]. There is increasing evidence that chronic inflammation and immune dysregulation contributes to accelerated atherogenesis and plays a role in all stages of atherosclerosis [7]. . Both RA and atherosclerosis are complex polygenic diseases with shared disease mechanism. There is increasing evidence that chronic inflammation and immune dysregulation contributes to accelerated atherogenesis and plays a role in all stages of atherosclerosis [7].

An approach to assess the presence and extent of subclinical atherosclerosis is carotid ultrasonography. Carotid intima-media thickness (CIMT) is a simple, reliable, inexpensive, non-invasive marker that is increasingly being used to detect subclinical atherosclerosis and has been recommended by the American Heart Association (AHA), American Society of Echocardiography (ASE) and Society for Vascular Medicine (SVM) as a screening test for heart disease in apparently healthy individuals[8,9].

Coronary Arterial Calcification (CAC), as a subclinical measure of atherosclerosis, measured by Computed Tomography (CT), is closely associated with the degree of atherosclerotic plaque , and is strongly predictive of cardiovascular events . Coronary Artery Calcification Score (CACS) assessed by the multi-detector CT (MDCT) scan was reported to be useful in the assessment of the extension and severity of atherosclerosis in vascular beds[10].

METHODS

Patients : 100 rheumatoid arthritis patients with no history of cardiovascular events recruited from rheumatology and rehabilitation Zagazig University who were seen over 1-year period were included in the present study. All the patients fulfilled the 1987 American College of
Rheumatology classification criteria for RA and also fulfilled the 2010 classification criteria for RA [11,12]. Patients with diabetes and chronic renal disease were excluded from the study .

Control : 50 apparently healthy subject match patients for age and sex and body mass index

Measurements: *Clinical data collection*: Data were obtained on traditional cardiovascular risk factors, such as age, body mass index, hypertension, hypercholesterolemia, smoking, and history of cardiovascular disease. Clinical variables reflecting RA disease activity were measured, including patient's global assessment, physician's global
assessment, acute-phase reactant levels ,patient's assessment of pain, numbers of tender and swollen joints using DAS28.

Framingham Coronary Heart Disease Risk Score

We calculate Framingham Risk Score is a gender-specific algorithm used to estimate the 10-year cardiovascular risk of an individual. Individuals with **low risk** have 10% or less CHD risk at 10 years, with **intermediate risk** 10-20%, and with **high risk** 20% or more. The first Framingham Risk Score included age, sex, LDL cholesterol, HDL cholesterol, blood pressure (and also whether the patient is treated or not for his/her hypertension), diabetes, and smoking . Updated version was modified to include dyslipidemia, age range, hypertension treatment, smoking, and total cholesterol, and it excluded diabetes, because Type 2 diabetes meanwhile was considered to be a CHD Risk Equivalent, having the same 10-year risk as individuals with prior CHD. Patients with Type 1 diabetes were considered separately with slightly less aggressive goals; while at increased risk, no study had shown them to be at equivalent risk for CHD as those with previously diagnosed coronary disease or Type 2 diabetes. **10-year risk in women %**: Points total: Under 9 points: <1%. 9-12 points: 1%. 13-14 points: 2%. 15 points: 3%. 16 points: 4%. 17 points: 5%. 18 points: 6%. 19 points: 8%. 20 points: 11%. 21=14%, 22=17%, 23=22%, 24=27%, >25= Over 30%
10-year risk in men %: Points total: 0 point: <1%. 1-4 points: 1%. 5-6 points: 2%. 7 points: 3%. 8 points: 4%. 9 points: 5%. 10 points: 6%. 11 points: 8%. 12 points: 10%. 13 points: 12%. 14 points: 16%. 15 points: 20%. 16 points: 25%. 17 points or more: Over 30% [13]

Laboratory methods. We measured laboratory parameters
at the time of the ultrasound scan. Total cholesterol, triglyceride, and high-density lipoprotein cholesterol levels were determined by the enzymatic method . Low-density lipoprotein (LDL) cholesterol levels. The erythrocyte sedimentation rate (ESR) was measured using the modified Westergren method, and C-reactive protein (CRP) levels and rheumatoid factor (RF) positivity were measured by nephelometry (Beckman, Brea, CA).

CARTOID ULTRASONGRAPHY :

Ultrasound Protocol

Ultrasound examination was performed with the use of a 7.5-MHz linear ultrasound transducer (Hitachi, EUB 5500) by a single trained radiologist. With this technique, 2 parallel echogenic lines separated by an anechoic space can be visualized at levels of the artery wall. The distance between the 2 lines gives a reliable index of the thickness of the intimal-medial complex Subjects were examined in the supine position. Ultrasound scans of the right and left last distal centimeter of common carotid arteries and bifurcation and of the first proximal centimeter of internal carotid arteries in 3 different projections (anterior, lateral, and posterior) were performed. All measurements were made at the time of scanning on unfrozen images of longitudinal scans by using the machine's electronic caliper. Six carotid segments for each projection (near and far walls of bulb and internal and common carotid arteries) were examined. The maximal IMT value of each segment was measured.

Coronary calcium scoring technique

Coronary CTA was performed using a 128-slice CT scanner (Ingenuity Core 128, Philips). Before injecting contrast medium, non-contrasted cardiac CT was performed in a longitudinal scan field from tracheal carina down to the diaphragm. The corresponding images for calcium scoring were reconstructed with a slice width of 2.5–3 mm and slice interval of 1.25–1.5 mm and the tube voltage was 120 kVp. Total calcium score was calculated using dedicated Vitrea2 software. Calcium score based on the Agatston method was defined as the presence of a lesion with an area greater than 1 mm^2, and peak intensity greater than 130 Hounsfield Units, which was automatically identified and marked with color by the software. All lesions were added to calculate the total calcium score with the Agatston method

Method of calculation

The calculation is based on the weighted density score given to the highest attenuation value (HU) multiplied by area of the calcification speck.

Density factor:

- 130-199 HU: 1
- 200-299 HU: 2
- 300-399 HU: 3
- 400+ HU: 4

For example, if a calcified speck has maximum attenuation value of 400 HU and occupies 8 sq mm area, then its calcium score will be 32.

The score of every calcified speck is summed up to give the total calcium score.

Grading of coronary artery disease (based on total calcium score)

- no evidence of CAD: 0 calcium score
- minimal: 1-10
- mild: 11-100
- moderate: 101-400
- severe: >400

[14].

Table 1 Clinical characteristics (risk factors for coronary artery disease)
of the study participants are summarized in Table 1. There was no significant difference in these variables between RA patients and controls except for CRP, Total cholesterol, LDL cholesterol, Triglycerides.

Table 2 There were significant difference between patients and control regarding the CIMT , Carotid plaque ,coronary artery calcifications and Framingham score .

Table 3 Showed positive strong correlation between age at the time of study and the carotid artery IMT in patients with RA was observed (r _ 0.522, *P* _ 0.001). Also, a significant disease duration (r _ 0.277, *P* _ 0.03), total cholesterol (r _ 0.433, *P* _ 0.001), and LDL cholesterol (r _ 0.343, *P* _0.01) was found. Positive correlation between Framingham risk score carotid artery IMT in patients with RA was observed . there was significant correlation between carotid IMT and DAS28 score, the laboratory markers of inflammation assessed at the time of the study, but there weren't significant correlation between CIMT the corticosteroid dose, Systolic blood pressure, Diastolic blood pressure and triglycerides

Discussion

Evidence continue to accumulate indicating that patients with RA present an increased risk of CV mortality and morbidity. The factors involved in the pathogenesis of increased CV disease are complex and multi-factorial involving complex inflammatory mechanism leading to accelerated and premature atherosclerosis. [15].

In our study we found significant difference between patients and control in ESR ,CRP, Total cholesterol, Triglycerides .In this we match the result of several studies. Some of these studies have reported higher TC, and LDL-C/HDL-C ratios in active disease than in the general population [15,16,17,18]. It has even been suggested that RA and atherosclerosis may share a common predisposition factor [19,20,21]. CRP is the common denominator for both diseases. CRP, which increases in active disease, may contribute to atherosclerosis because it stimulates macrophages to produce tissue factor, a procoagulant that is found in atherosclerotic plaques [22]

We found that the RA patients showed a significantly higher CCA-IMT than the controls . In many studies (22-27), they found that the RA patients showed a significantly higher CCA-IMT than controls , our study showed an increased of carotid plaques in the RA patients as compared to controls , many studies[27-34] showed an increased prevalence of carotid plaques in the RA patients as compared to controls.

We found that patients with RA had higher Framingham risk scores compared with control subjects .in this we agreed with the results of chung and his colleagues [32] who reported that patients with long-standing RA had higher Framingham risk scores compared with patients with early disease and control subjects.

CT studies have also confirmed that coronary-artery calcification occurs more frequently in patients with RA patients than controls. This match the result of Gile and his colleagues [33] who founded that CAC prevalence was slightly higher in the RA group.

Our study Showed positive strong correlation between age at the time of study and the carotid artery IMT in patients with RA was observed Also, a significant correlation between disease duration and carotid artery IMT in patients with RA, Our results are similar to other studies worldwide[33,34,35]We could come across study from India. Grover et al[34] reported subclinical atherosclerosis in one-third of their patients with RA using CIMT. Fifty two of the 57 patients in their cohort were women with an average age of 41.52 ± 7.53 years and an average disease duration of 8.03 ± 5.48 years. Abnormal IMT in their study correlated with age, disease duration. Our results didn't match the results of Arts and his collaegues[37] who founded that Disease duration does not appear to independently affect the risk of CVD.

Our study Showed positive strong correlation between carotid artery IMT and (DAS28, CRP level, ESR) at the time of study and the in patients with RA was observed that can be explained that In RA, primary site of inflammation is synovial tissue, from which cytokines can be released into systemic circulation. These circulating cytokines alter function of distant tissues, including adipose, skeletal muscle, liver, and vascular endothelium, to generate a spectrum of proatherogenic changes that include insulin resistance, characteristic dyslipidemia, prooxidative effects, and endothelial dysfunction and damage. Numerous studies report an inverse association between inflammatory markers (CRP or erythrocyte sedimentation rate [ESR]) and HDL cholesterol or its main protein, apolipoprotein AI [35]

This study has collated evidence to suggest that the systemic inflammatory response in RA is central to the accelerated atherogenesis so we think that long-term suppression of the systemic inflammatory response in RA should lessen CHD risk, Our results support the use of carotid US in the assessment of CV risk in patients with RA. Coronary artery calcification score also useful in assessment of CV risk in patients with RA.

Table 1. Demographic, clinical, laboratory findings of100 patients with Rheumatoid arthritis (RA) and 50 matched controls

	Patients (n 100)	CONTROL n0=50	P
Age	48.8± 12.4	45.8± 12.1	.16
Men/women	31/69	11/19	
Body mass index, kg/m2	25.6± 1.9	25.4± 2.1	.56
DAS28 score	2.4± 0.7	Nil	--
CRP level, mg/lite	20.2± 28.9	0.23 ± 0.34	.00*
ESR, mm/hour	29.3± 23.5	11.5±12	.04
Total cholesterol	194.7± 31.5	11.9 ± 36.2	.00*
HDL cholesterol	53.8± 11.9	51.3 ±14.8	.27
LDL cholesterol	116.8± 24.7	132.5 ± 33.9	.00*
Triglycerides	190.0± 50.9	139.4±_ 87.6	.00*
Smoker	10 (10%)	4 (8%)	.92
Presence of extra-articular manifestations	39%) (39	) .0(00	.00*
HAQ	1.2 ±0.3	Nil	.00*
Pain ,0-10 visual analog scale	3.3±2.2		.00*
Patient's global assessment, 0–10 scale	4.4±2.6		.00*
Physician's global assessment, 0–10 scale	3.3 ± 2.2		.00*
Antirheumatic treatment, (%) of patients Methotrexate Other DMARDs Prednisolone more than 10 mg/day	87.0)(87 55(55.0) 40(40,0)		

Table 2

	Patients	Control	
Carotid IMT, mm Carotid intima-media thickness >0.90 mm n(%)	**(0.87 ± 0.09 mm** 15(15.0)	**0.58±0.14 mm;** 4(8.0)	***0.00****
Carotid plaques, no. (%)	60(60)	12(24.0)	0.00*
Coronary artery calicifications Normal CACS=0 CACS=0-100(mild CACS=101-400 CACS >400	 55(55.0) 25(25.0) 13(13.0) 7(7.0)	 40(80.0) 6(12.0) 3(6.0) 1(2.0)	 0.00*
Framingham risk score %	12± 9 Mild risk 64(64) Moderate risk 29(29) High risk 7(7)	7±5 Mild risk 43(86) Moderate risk 7 (7)	0.00*

Table 3 . correlation of carotid artery intima media Thickness with selected variables in 100 patients with rheumatoid arthritis.

	R	P	
Age	0.522	0.00*	
Disease duration	0.277	0.03*	
DAS28	0.342	0.000*	
Systolic blood pressure	0.031	0.74	
Diastolic blood pressure	0.048	0.74	
ESR	0.318	0.00*	
CRP	0.299	0.04*	
Total cholesterol	0.433	0.00*	
HDL cholesterol	-0.044	0.82	
LDL cholesterol	0.343	0.01*	
Triglycerides	0.057	0.56	
prednisone dose	0.030	0.84	
Framingham risk score	0.344	0.00*	

Table 4
Correlation between the Coronary Artery Calcification Score (CACS) and the carotid intima-media thickness (cIMT) in 100 patients with rheumatoid arthritis.

CACS	cIMT ≤0.90 mm n (%)(81)	cIMT >0.90 mm n19 (%)	
0(55)	50 (61.7)	5 (26.3)	.01*
1-100(2	18/25(72.0)	7/25(28.0)	.30
>101-400	8/13(61.0)	6/13(39.0)	.04*
	5/7(71.0)	2/7(29.0)	.86
>1(45)	31 (38.3)	14 (73.7)	.01*

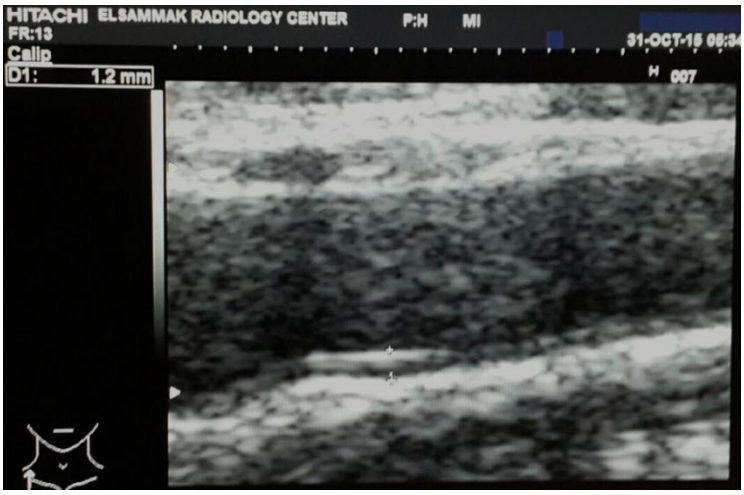

Image (1)
Longitudinal ultrasound scan of common carotid artery shows increased intima media thickness (1.2 mm).

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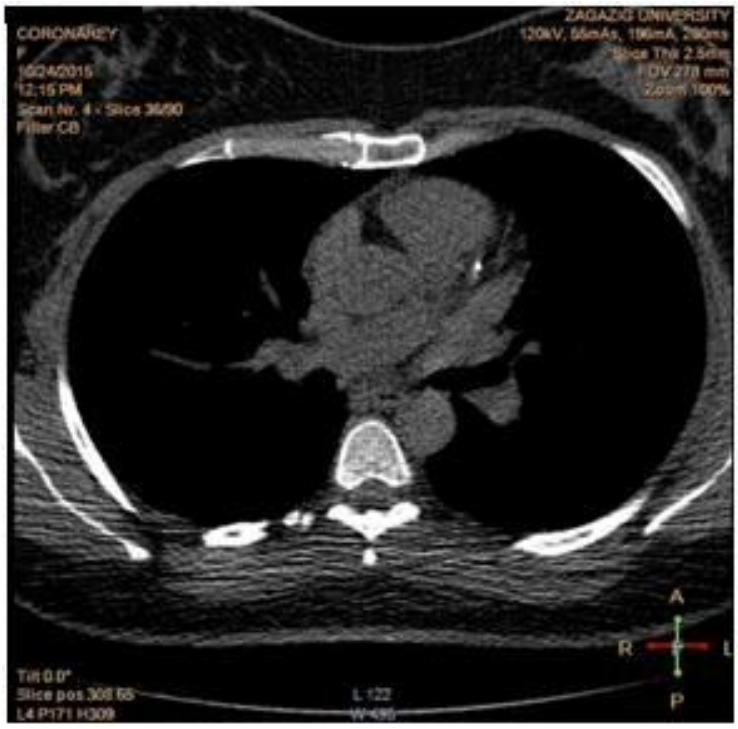

Image 2
Non enhanced axial CT section shows calcified plaque at left anterior descending branch with calcium score=36.

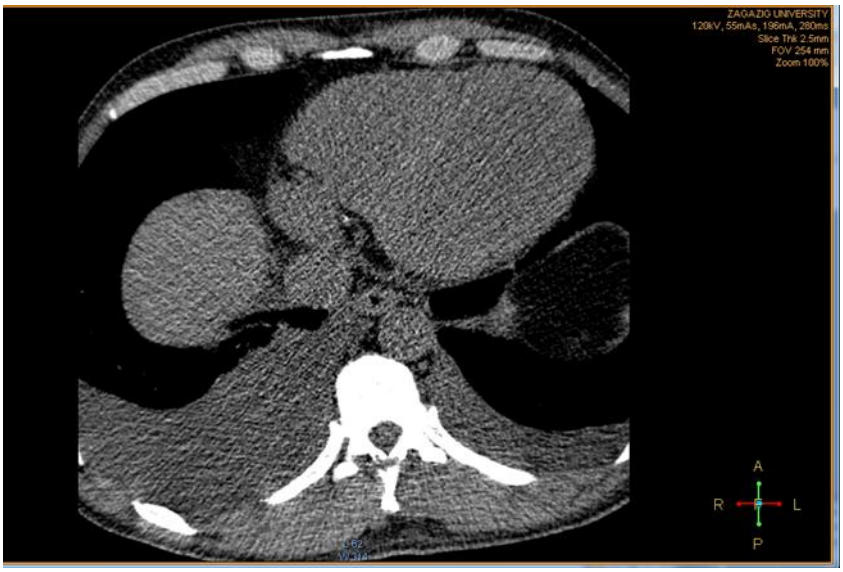

Image 3
Non enhanced axial CT section shows calcified plaque at right coronary artery with calcium score=25
Also there is bilateral pleural effusion

Conclusion

Patients with RA have higher Framingham cardiovascular risk scores . our data indicate that RA patients have an ultrasonic marker of early atherosclerosis. This finding is consistent with an increased risk for atherosclerosis.The use of coronary-artery calcium scores may add information to the assessment of cardiovascular risk in patients with RA and may lead to better guidelines for therapeutic interventions in this patient population.

Refrences

1. Symmons DP, Jones MA, Scott DL, Prior P. Longterm mortality outcome in patients with rheumatoid arthritis: early presenters continue to do well. J Rheumatol 1998;25:1072–7.

2. Wallberg-Jonsson S, Ohman ML, Dahlqvist SR. Cardiovascular morbidity and mortality in patients with seropositive rheumatoid arthritis in Northern Sweden. J Rheumatol 1997;24:445–51.

3. Mutru O, Laakso M, Isomaki H, Koota K. Ten year mortality and causes of death in patients with rheumatoid arthritis. BMJ 1985; 290:1797–9.

4. Isomaki HA, Mutru O, Koota K. Death rate and causes of death in patients with rheumatoid arthritis. Scand J Rheumatol 1975;4: 205–8.

5. Erhardt CC, Mumford PA, Venables PJ, Maini RN. Factors predicting a poor life prognosis in rheumatoid arthritis: an eight year prospective study. Ann Rheum Dis 1989;48:7–13.

6. Park YB, Lee SK, Lee WK, Suh CH, Lee CW, Lee CH, et al. Lipid profiles in untreated patients with rheumatoid arthritis. J Rheumatol 1999;26:1701–4.

7. Meune C, Touzé E, Trinquart L, Allanore Y (2009) Trends in cardiovascular mortality in patients with rheumatoid arthritis over 50 years: a systematic review and meta-analysis of cohort studies. Rheumatology (Oxford) 48: 1309-1313.

8.Greenland P, Alpert JS, Beller GA, Benjamin EJ, Budoff MJ, 8. Fayad ZA, *et al*. 2010 ACCF/AHAguideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2010; *122* : e584-636.

9. Stein JH, Korcarz CE, Hurst RT, Lonn E, Kendall CB, 9. Mohler ER, *et al*. American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. *J Am Soc Echocardiogr* 2008; *21* : 93-111.

10. 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 Med2009;266:445–52.

11.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.

12. Aletaha D, Neogi T, Silman AJ, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2010;69:1580–8.

13. D'Agostino RB Sr, Grundy S, Sullivan LM, Wilson P. JAMA. 2001. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. Jul 11;286(2):180-7.

14.van der Bijl N, Joemai RM, Geleijns J et-al. Assessment of Agatston coronary artery calcium score using contrast-enhanced CT coronary angiography. AJR Am J Roentgenol. 2010;195 (6): 1299-305.

15.Situnayake R, Kitas G: Dyslipidemia and rheumatoid arthritis. Ann Rheum Dis 1997, 56:341-342

16.Lazarevic MB, Vitic J, Mladenovic V, Myones BL, Skosey JL, Swedler WI: Dyslipoproteinemia in the course of active rheumatoid arthritis. Semin Arthritis Rheum 1992, 22:172-178.
17.Del Rincon ID, Williams K, Stern MP, Freeman GL, Escalante A: High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors. Arthritis Rheum 2001, 44:2737-2745.

18. Dessein PH, Stanwix AE, Moomal Z: Rheumatoid arthritis and cardiovascular disease may share similar risk factors (Letter). Rheumatology 2001, 40:703-704.

19.Dessein PH, Stanwix AE, Joffe BI: Cardiovascular risk in rheumatoid arthritis versus osteoarthritis: acute phase response related decreased insulin sensitivity and high-density lipoprotein cholesterol as well as clustering of metabolic syndrome features in rheumatoid arthritis. Arthritis Res 2002, 4:R5

20. Pasceri V, Yeh ET: A tale of two diseases: atherosclerosis and rheumatoid arthritis. Circulation 1999, 100:2124-2126

21. Jonsson SW, Backman C, Johnson O, Karp K, Lundstrom E, Sundqvist KG: Increased prevalence of atherosclerosis in patients with medium term rheumatoid arthritis. J Rheumatol 2001, 28:2597-2602.

22.Georgiadis AN, Voulgari PV, Argyropoulou MI, et al. Early treatment reducesthe cardiovascular risk factors in newly diagnosed rheumatoid arthritis patients. Semin Arthritis Rheum 2008; 38: 13–19.

23. Gerli R, Sherer Y, Vaudo G, et al. Early atherosclerosis in rheumatoid arthritis: effects of smoking on thickness of the carotid artery intima media. Ann NY Acad Sci 2005; 1051: 281–290.

24.Hannawi S, Haluska B, Marwick TH, et al. Atherosclerotic disease is increasedin recent-onset rheumatoid arthritis: a critical role for inflammation. Arthritis Res Ther 2007; 9: R116.

25. Lee JH, Cho KI, Kim SM. Carotid arterial stiffness in patients with rheumatoid arthritis assessed by speckle tracking strain imaging: its association with carotid atherosclerosis. Clin Exp Rheumatol 2012; 30: 720–728

26. Mahajan V, Handa R, Kumar U, et al. Assessment of atherosclerosis by carotid intimomedial thickness in patients with rheumatoid arthritis. J Assoc Physicians India 2008; 56: 587–590.

27. Akrout R, Fourati H, Mnif E, et al. Increased cardiovascular risk and premature atherosclerosis in rheumatoid arthritis. Ann Cardiol Angeiol 2012; 61: 267–273.

29. Alkaabi JK, Ho M, Levison R, et al. Rheumatoid arthritis and macrovasculardisease. Rheumatology 2003; 42: 292–297.

30. Carotti M, Salaffi F, Mangiacotti M, et al. Atherosclerosis in rheumatoid arthritis: the role of high-resolution B mode ultrasound in the measurement of the arterial intima-media thickness. Reumatismo 2007; 59: 38–49.

31. Zampeli E, Protogerou A, Stamatelopoulos K, et al. Predictors of new atherosclerotic carotid plaque development in patients with rheumatoid arthritis: a longitudinal study. Arthritis Res Ther 2012; 14: R44.

32-Cecilia P Chung, Annette Oeser, Ingrid Avalos, Tebeb Gebretsadik, Ayumi Shintani, Paolo Raggi, et al. Utility of the Framingham risk score to predict the presence of coronary atherosclerosis in patients with rheumatoid arthritis. Arthritis Res Ther. 2006; 8(6): R186.

33- Jon T Gile, Moyses Szklo, Wendy Post, Michelle Petri, Roger S Blumenthal. Coronary arterial calcification in rheumatoid arthritis: comparison with the Multi-Ethnic Study of Atherosclerosis. Arthritis Res Ther. 2009; 11(2): R36.

34. Grover S, Sinha RP, Singh U, Tewari S, Aggarwal A, Misra R. Subclinical atherosclerosis in rheumatoid arthritis in India. J Rheumatol 2006;33:244–7.

35- Kumeda Y, Masaakilnaba, Hitoshi G, Nagata M, Henmi Y, Furumitsy Y, et al. Increased thickness of the arterial intima-media detected by ultrasonography in patients with rheumatoid arthritis. Arthritis Rheum 2002;46:1489-97. 23

36. Rodriguez G, Sulli A, Cutolo M, Vitali P, Nobili F. Carotid atherosclerosis in patients with rheumatoid arthritis: A preliminary case-control study. Ann NY Acad Sci 2002;966:478-82.

37. Elke EA Arts **,**Jaap Fransen , Alfons A den Broeder **.**Calin D Popa,Piet L C M van Riel . The effect of disease duration and disease activity on the risk of cardiovascular disease in rheumatoid arthritis patients. Ann Rheum Dis doi:10.1136/annrheumdis-2013.