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Original Article

A comparison of vascular inflammation in psoriasis, rheumatoid arthritis, and healthy subjects by FDG-PET/CT: a pilot study

Shawn Rose[1,2], Nikhil H Sheth[3], Joshua F Baker[4], Alexis Ogdie[4], Anna Raper[3], Babak Saboury[5], Thomas J Werner[5], Preethi Thomas[4], Abby Vanvoorhees[6], Abass Alavi[5], Drew A Torigian[5], Joel M Gelfand[6,7,8], Nehal N Mehta[1,3,8]

[1]Section of Inflammation and Cardiometabolic Diseases, National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health, Bethesda, MD; [2]National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Institutes of Health, Bethesda, MD; [3]Cardiovascular Institute, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; [4]Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; [5]Department of Radiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; [6]Department of Dermatology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; [7]Department of Epidemiology and Biostatistics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; [8]Center for Clinical Epidemiology and Biostatistics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

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Abstract: Objective: Psoriasis (PSO) and rheumatoid arthritis (RA) increase cardiovascular diseases (CVD) beyond traditional risk factors. Vascular inflammation has previously been demonstrated to be present in PSO and RA using [18F]-fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) imaging. However, vascular inflammation has not been compared in these two disorders relative to a healthy reference population. Thus, vascular inflammation was quantitatively assessed in patients with PSO (n=10), RA (n=5), and healthy subjects (n=10) using FDG-PET/CT. Methods: FDG-PET/CT mean standardized uptake value (SUVmean) was determined slice by slice within the ascending, aortic arch, descending thoracic, suprarenal abdominal, and infrarenal abdominal aorta, and the mean metabolic volumetric product (MVPmean) was then calculated for each aortic subsegment. Plasma lipids and metabolic and inflammatory markers were also assessed. Results: CVD risk profiles were largely similar across groups. After adjustment for CV risk factors, regional aortic vascular inflammation based on MVPmean was elevated for both PSO (beta coefficients 0.31-1.47, $p<0.001$) and RA (beta coefficients 0.15-0.69, $p<0.05$) compared to healthy subjects. Conclusions: These observations using FDG-PET/CT to estimate vascular inflammation support epidemiological findings of premature atherosclerosis in PSO and RA. The use of FDG-PET/CT to investigate vascular inflammation across systemic inflammatory diseases warrants further examination in larger study populations.

Keywords: Psoriasis, rheumatoid arthritis, atherosclerosis, vascular inflammation, FDG-PET/CT

Introduction

Atherosclerosis is a chronic, progressive form of vascular inflammation that can lead to life-threatening cardiovascular (CV) events such as myocardial and cerebrovascular infarction [1]. Psoriasis (PSO) and rheumatoid arthritis (RA) are systemic immune-mediated disorders that are characterized by premature cardiovascular disease (CVD) beyond traditional CV risk factors [2]. Importantly, both PSO [3] and RA [4] reduce life expectancy, which has largely been attributed to CVD. Subclinical vascular inflammation has previously been demonstrated in PSO [5, 6] and RA [7] using [18F]-fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT). FDG-PET/CT assesses macrophage activity in atherosclerotic plaques [8], allowing highly sensitive localization and quantification of vascular inflammation in large vessels [5, 9]. Further, focal arterial inflammation detected by FDG

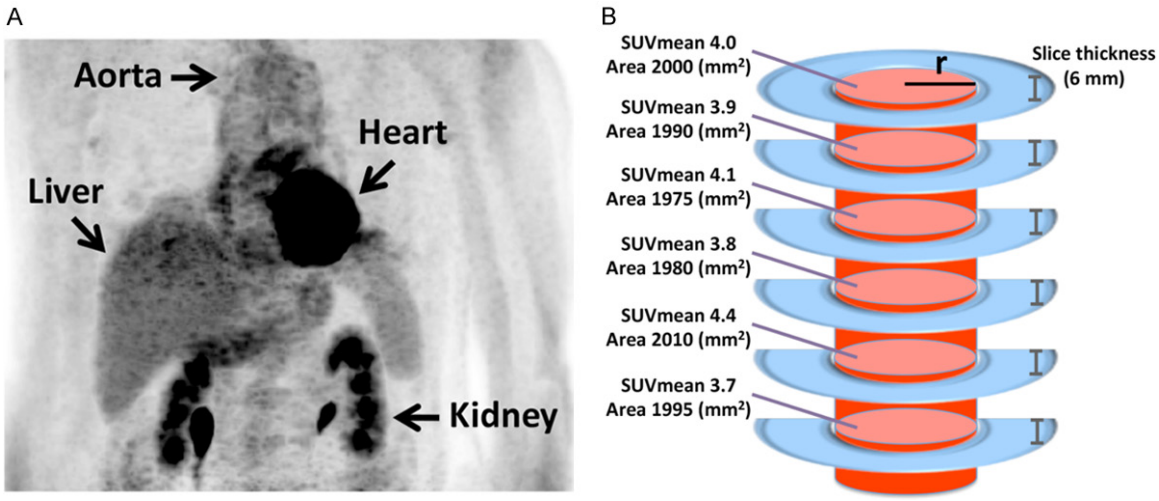

Figure 1. Quantification of aortic vascular inflammation by FDG-PET/CT. A: FDG-PET/CT Maximum Intensity Projection (MIP) image delineating areas of intense metabolic activity (heart) or FDG excretion (kidney and urinary collecting system). The liver and aortic arch demonstrate abnormally high FDG uptake in this patient with a long-standing history of psoriasis. B: Diagrammatic representation of mean metabolic volumetric product (MVPmean) measurements of the aorta (red cylinder) using FDG-PET/CT. Regions of interest (ROIs) outlining sequential slices of the aorta (pink circle) are delineated. The radius (r) of a representative circular ROI is indicated (black line). Blue rings depict 6 mm thick (gray brackets) PET/CT slices. The mean standardized uptake value (SUVmean) and ROI area (πr^2) for each slice are auto-calculated by the Extended Brilliance Workstation (EBW) software. ROI volume (mm^3) per slice is calculated by multiplying ROI area (mm^2) by slice thickness (mm). The MVPmean is then derived by multiplying SUVmean by ROI volume (mm^3) for each slice. In this example, the MVPmean for the uppermost slice is 4.0 x 2000 mm^2 x 6 mm = 48,000 mm^3.

PET/CT has been shown to precede the development of calcified atherosclerotic plaque in the vessel wall [10]. While FDG-PET/CT has been used to characterize vascular disease in PSO and RA, it is unknown whether the presence, location, and severity of vascular inflammation differ between these disorders, relative to a healthy reference population. Comparison of vascular inflammation across disease states may elucidate whether similar or distinct mechanisms contribute to CVD in systemic inflammatory disorders. Here, for the first time to our knowledge, we utilized FDG-PET/CT to examine vascular inflammation in PSO and RA without known CVD relative to a healthy reference population.

Materials and methods

Study population

FDG-PET/CT was performed in patients with PSO (n=10), RA (n=5), and healthy subjects (n=10). Eligibility criteria included age 18 to 70 years, a diagnosis of plaque PSO involving >10% body surface area (BSA) confirmed by a dermatologist or RA diagnosed by a rheumatologist (American College of Rheumatology 2010 Criteria) [11]. This study was designed to demonstrate the feasibility of applying FDG-PET/CT to quantify vascular inflammation in PSO and RA compared to a healthy population. Thus, we consecutively enrolled patients including those undergoing active treatment with phototherapy, topical therapy or stable doses (not changed within 12 weeks of study enrollment) of oral systemic medications (e.g., methotrexate) or biologic agents. Exclusion criteria included states that are known to increase either systemic or vascular inflammation such as diabetes mellitus, known clinical history of CVD, uncontrolled hypertension (defined as systolic blood pressure >180 mm Hg or diastolic blood pressure >95 mm Hg), >2 alcoholic beverages per day, non-skin malignant disease within 5 years, positive human immunodeficiency virus status, major surgery within 3 months, history of intravenous drug use, or active infection within the preceding 72 hours. Healthy subjects included those participants without any diagnosis of illness by review of medical records, including LDL <190, fasting

Table 1. Patient characteristics

	PSO	RA	Controls	
	Median (IQR) n=10	Median (IQR) n=5	Median (IQR) n=10	*p* value
Age	48 (42-53)	40 (19-46)	45 (38-50)	0.177, 0.682, 0.296
Male, count (%)	8 (80%)	2 (40%)	9 (90%)	0.251, 0.500, 0.077
Disease Duration (years)	15 (10-27)	8 (4-16)	-	0.269
Psoriatic Arthritis, count (%)	3 (30%)	-	-	-
Body Surface Area (BSA), (%)	20 (13-32)	-	-	-
Psoriasis Area and Severity Index (PASI)	12.1 (9.2-17.2)	-	-	-
RA Severity (DAS28-CRP)	-	3.31 (3.13-3.56)	-	-
Systemic Therapy, count (%)	2 (20%)	5 (100%)	-	0.007
Biologic Therapy, count (%)	0 (0%)	4 (80%)	-	0.004
Phototherapy, count (%)	2 (20%)	-	-	-
Topical Therapy, count (%)	6 (60%)	-	-	-
Anti-CCP Positivity, count (%)	-	5 (100%)	-	-
High sensitivity C-reactive protein (g/dL)	2.5 (2-13)	3.9 (3.5-5.2)	0.4 (0.4-1.6)	0.660, 0.033, 0.010
Tobacco Use, count (%)	2 (20%)	0 (0%)	0 (0%)	0.524, 0.474, 1.000
Body Mass Index	30.6 (27.87-37.2)	22.5 (18.9-24.1)	29.6 (24.1-30.0)	0.050, 0.424, 0.143
Fasting Blood Glucose (mg/dL)	87 (79-92)	86 (71-89)	91 (81-97)	0.580, 0.487, 0.285
Systolic Blood Pressure (mm Hg)	130 (121-137)	131 (116-136)	122 (120-133)	0.062, 0.595, 0.947
Diastolic Blood Pressure (mm Hg)	80 (71-84)	72 (70-84)	74 (72-80)	0.854, 0.682, 0.688
Diagnosed Hypertension, count (%)	2 (20%)	1 (20%)	2 (20%)	1.000, 1.000, 1.000
Anti-Hypertensive Therapy, count (%)	1 (10%)	1 (20%)	2 (20%)	1.000, 0.582, 1.000
Total Cholesterol (mg/dL)	209 (154-229)	169 (147-175)	188 (151-206)	0.270, 0.248, 0.212
Triglycerides (mg/dL)	169 (94-191)	58 (46-93)	135 (65-262)	0.020, 0.657, 0.079
High-Density Lipoprotein (mg/dL)	38 (36-39)	58 (53-70)	48 (44-50)	0.019, 0.109, 0.023
Low-Density Lipoprotein (mg/dL)	104 (90-161)	80 (78-87)	118 (67-123)	0.057, 0.423, 0.240
Statin Therapy, count (%)	2 (20%)	0 (0%)	1 (10%)	0.524, 1.000, 1.000

IQR=Interquartile range; (-)=not applicable. Diabetes mellitus, a traditional cardiovascular disease risk factor, is omitted from this table, as it was an exclusion criterion in the study. Anti-CCP denotes anti-cyclic citrullinated peptide antibodies. Systemic therapy denotes active methotrexate and/or prednisone use. Biologic therapy denotes active TNF antagonist (PSO or RA) or anti-IL-12/23 receptor (PSO) use. Reported *p* values are for comparisons of PSO vs. RA, PSO vs. controls, and RA vs. controls, respectively.

glucose <126 and BMI <30. The first 6 PSO and 4 healthy subjects were part of a previously described FDG-PET/CT study cohort [6] published as a pilot study.

FDG-PET/CT

Whole-body FDG-PET/CT scans were performed using a standardized protocol [6]. Images were qualitatively and quantitatively reviewed using dedicated PET/CT image analysis software (Extended Brilliance Workstation (EBW); Philips Healthcare, Bothell, Washington) according to published methods [5]. In brief, circular 2-dimensional regions of interest (ROI) were manually drawn around the external aortic contour of serial transverse sections extending from the aortic root to the iliac bifurcation. Mean standardized uptake values (SUVmean) and areas for each ROI in successive slices were auto-calculated using EBW software. The mean metabolic volumetric product (MVPmean), defined as SUVmean per slice x ROI area (in mm^2) x slice thickness (in mm), was then derived for each slice. MVPmean corresponds to the metabolic activity within each slice of the aorta (**Figure 1**), which was divided into 5 segments: ascending, aortic arch, descending thoracic, suprarenal abdominal, and infrarenal abdominal aorta.

Serum lipid determination

Fasting serum levels of total, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) cholesterol, triglyceride, glucose and high sensitivity C-reactive protein were measured in a clinical laboratory.

Table 2. PSO and RA increase aortic vascular inflammation

Region	PSO	RA	Controls	*p* value*
Ascending Aorta	1.49	1.49	1.37	0.0001
	[0.025]	[0.024]	[0.017]	
	(0.241)	(0.180)	(0.160)	
Aortic Arch	1.42	1.39	1.27	0.0001
	[0.027]	[0.035]	[0.022]	
	(0.218)	(0.190)	(0.160)	
Descending Thoracic Aorta	1.42	1.43	1.28	<0.0001
	[0.011]	[0.012]	[0.012]	
	(0.207)	(0.180)	(0.210)	
Suprarenal Abdominal Aorta	1.39	1.31	1.37	0.1067
	[0.014]	[0.016]	[0.012]	
	(0.194)	(0.110)	(0.150)	
Infrarenal Abdominal Aorta	1.35	1.34	1.28	0.0002
	[0.013]	[0.021]	[0.009]	
	(0.222)	(0.150)	(0.140)	

Mean SUV values [standard error] (standard deviation) are reported for each aortic location in PSO, RA, or control patients. *p values are reported for PSO vs. Controls; p values for RA vs. Controls are less than or equal to each of these values.

Statistical analysis

Continuous variables were compared using Mann-Whitney U tests and Fisher's exact tests were employed for dichotomous variable comparisons. Linear regression analysis was performed with FDG-PET/CT measures (MVPmean) as the dependent variable and CV risk factors (age, gender, hypertension, LDL, and body mass index [BMI]) and disease state (PSO vs. RA) as independent variables. Both fixed and random effects regression models were also performed to accommodate within-patient correlation of MVPmean. Because there were no observed differences in estimates for PSO or RA using fixed and random effects modeling, we report beta coefficient and *p*-values from the fixed effects models, after adjustment for multiple comparisons. All analyses were performed with Stata 12 statistical software (StataCorp, College Station, Texas). Study approval was obtained from the institutional review board in accordance with the Declaration of Helsinki. Written informed consent was obtained from all study participants.

Results

A proof-of-principle study was performed in patients with PSO, RA, and healthy subjects to compare vascular inflammation among these populations using FDG-PET/CT. Patients with PSO had a median disease duration of 15 years (interquartile range [IQR] 10-27), median BSA of 20 (IQR 13-32), a median Psoriasis Area and Severity Index of 12.1 (IQR 9.2-17.2, **Table 1**) and were mostly (60%) only on topical therapy (**Table 1**). Patients with RA had the disease for a median of 8 years (IQR 4-16), were positive for anti-cyclic citrullinated peptide antibodies, had a median DAS28-CRP of 3.31 (IQR 3.13-3.56, **Table 1**) and were all receiving systemic and/or biologic therapy (**Table 1**). Systemic (100% vs. 20%, p=0.007) and biologic (80% vs. 0%, p=0.004) therapy was more frequent in the RA than the PSO group (**Table 1**). CV risk factors were largely comparable among the study groups except as noted: BMI was greater in the PSO than the RA group and HDL levels were lower in the PSO group compared to either RA patients or healthy subjects (**Table 1**).

Areas of vascular inflammation were clearly delineated by FDG-PET/CT imaging (**Figure 1**). Analysis of aortic subsegments showed that SUVmean measurements were significantly greater in the ascending, aortic arch, descending thoracic, and infrarenal aortic segments in patients with PSO and RA, compared to healthy subjects (**Table 2**) in unadjusted analysis. Since volume-based measures more accurately define regional vascular inflammation [5], subsequent analyses were performed using MVPmean as the outcome variable. In multivariate regression analyses, both PSO and RA were associated with aortic MVPmean values after adjusting for CV risk factors, except in the aortic arch region (**Table 3**). Together, these findings suggest that PSO and RA are associated with greater vascular inflammation that can be measured by FDG-PET/CT.

Discussion

To our knowledge, this is the first study to compare vascular inflammation in PSO and RA relative to a healthy population. The magnitude of SUVmean increase (range 0.06-0.15) identified

Table 3. Vascular inflammatory burden is elevated in PSO and RA

	PSO vs. Controls		RA vs. Controls		PSO vs. RA	
Regression Factors	Age, Gender and BMI	Age, Gender, BMI, HTN and LDL-C	Age, Gender and BMI	Age, Gender, BMI, HTN and LDL-C	Age, Gender and BMI	Age, Gender, BMI, HTN and LDL-C
Region	Mean Value Product (MVP)					
Ascending Aorta	1.321 (<0.001)	1.467 (<0.001)	1.114 (<0.001)	0.694 (0.006)	-0.152 (0.661)	0.262 (0.464)
Aortic Arch	3.423 (0.263)	5.400 (0.092)	1.868 (0.153)	0.997 (0.434)	0.053 (0.990)	3.886 (0.442)
Descending Thoracic Aorta	0.549 (<0.001)	0.624 (<0.001)	0.320 (<0.001)	-0.088 (0.332)	0.170 (0.018)	0.418 (<0.001)
Suprarenal Abdominal Aorta	0.281 (<0.001)	0.314 (<0.001)	0.046 (0.710)	-0.119 (0.339)	0.256 (0.035)	0.510 (<0.001)
Infrarenal Abdominal Aorta	0.290 (<0.001)	0.337 (<0.001)	0.180 (0.004)	0.147 (0.035)	0.021 (0.736)	0.212 (0.002)

Multivariate regression analyses were performed for each inter-group comparison (PSO vs. Controls, RA vs. Controls, or PSO vs. RA). MVP was evaluated as the outcome variable in separate analyses for each aortic region. Dependent variables included in the model were age, gender, BMI, PSO and/or RA (left columns) or age, gender, BMI, HTN, LDL-C, PSO and/or RA (right columns). Beta coefficients (β) are reported for the effects of PSO or RA on vascular inflammation (MVP) after adjustment for CVD risk factors (age, gender, BMI, HTN, LDL-C).

in the aortic wall of patients with PSO and RA (compared to healthy subjects) corresponds to the degree of vascular inflammation observed over ~10 years of aging [12]. Significant vascular inflammation in PSO and RA was observed even after adjustment for CV risk factors. These findings are consistent with earlier reports demonstrating increased CV events in PSO [3] and RA [13] beyond traditional risk factors. Further, our data support the notion that vascular inflammation may be mechanistically linked to premature CVD in immune-mediated disorders. Indeed, observational studies have previously shown that future cardiovascular events can be predicted based on aortic and carotid inflammation identified by FDG-PET/CT [14-16].

This study demonstrates that FDG-PET/CT can be used to quantify vascular inflammation across disease states. Moreover, since FDG-PET/CT readily detects tissue inflammation [6], it may be an attractive modality for investigating regional and global inflammatory burden in the rheumatic diseases, skin diseases, and presumably other inflammatory disorders. Serial imaging could also potentially be performed to monitor disease course and response to treatment [17], and to relate clinical biomarkers to epidemiologic findings.

We acknowledge that the findings of this pilot study have limitations. The generalizability of the results may be affected by the small sample size, referral-based source of our participants, and single-center study design. Although analyses were adjusted for CV risk factors, incomplete measurement of other potential confounding variables, such as diet and exercise, may also have impacted the results. Effects of PSO, RA, hypertension and hyperlipidemia treatment could have resulted in an underestimate of the effect of disease on vascular inflammation measures, as no washout medication period was required prior to study enrollment. However, it is remarkable that although many of our PSO and RA patients were on systemic and/or biologic therapy, differences in vascular inflammation were readily detectible in both disorders compared to healthy subjects. Further, vascular inflammation was evident in a group of RA patients demonstrating only mild to moderate disease activity. Our findings warrant further exploration in larger-scale prospective studies.

Despite these limitations, our data suggest that FDG-PET/CT may be an important tool for CV risk estimation in patients with systemic inflammatory disorders. It is an operator-independent, quantitative, and reproducible technique [5] that could greatly enhance our assessment of inflammation in vascular, and potentially non-vascular tissues, in various inflammatory conditions.

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Disclosure of conflict of interest

The authors declare no competing conflict of interest.

Address correspondence to: Dr. Nehal N Mehta, Cardiovascular and Pulmonary Branch, NHLBI, 10 Center Drive, CRC, Room 5-5140, Bethesda, MD, 20892. Tel: 301-827-0483; Fax: 301-451-7093; E-mail: nehal.mehta@nih.gov

References

[1] Libby P. Inflammation in atherosclerosis. Arterioscler Thromb Vasc Biol 2012; 32: 2045-2051.

[2] Roman MJ and Salmon JE. Cardiovascular manifestations of rheumatologic diseases. Circulation 2007; 116: 2346-2355.

[3] Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ and Troxel AB. Risk of myocardial infarction in patients with psoriasis. JAMA 2006; 296: 1735-1741.

[4] Avina-Zubieta JA, Choi HK, Sadatsafavi M, Etminan M, Esdaile JM and Lacaille D. Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies. Arthritis Rheum 2008; 59: 1690-1697.

[5] Mehta NN, Torigian DA, Gelfand JM, Saboury B and Alavi A. Quantification of atherosclerotic plaque activity and vascular inflammation using [18-F] fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT). J Vis Exp 2012; e3777.

[6] Mehta NN, Yu Y, Saboury B, Foroughi N, Krishnamoorthy P, Raper A, Baer A, Antigua J, Van Voorhees AS, Torigian DA, Alavi A and Gelfand JM. Systemic and vascular inflammation in patients with moderate to severe psoriasis as measured by [18F]-fluorodeoxyglucose positron emission tomography-computed tomography (FDG-PET/CT): a pilot study. Arch Dermatol 2011; 147: 1031-1039.

[7] Maki-Petaja KM, Elkhawad M, Cheriyan J, Joshi FR, Ostor AJ, Hall FC, Rudd JH and Wilkinson IB. Anti-tumor necrosis factor-alpha therapy reduces aortic inflammation and stiffness in patients with rheumatoid arthritis. Circulation 2012; 126: 2473-2480.

[8] Rudd JH, Warburton EA, Fryer TD, Jones HA, Clark JC, Antoun N, Johnstrom P, Davenport AP, Kirkpatrick PJ, Arch BN, Pickard JD and Weissberg PL. Imaging Atherosclerotic Plaque Inflammation With [18F]-Fluorodeoxyglucose Positron Emission Tomography. Circulation 2002; 105: 2708-2711.

[9] Tawakol A, Migrino RQ, Hoffmann U, Abbara S, Houser S, Gewirtz H, Muller JE, Brady TJ and Fischman AJ. Noninvasive in vivo measurement of vascular inflammation with F-18 fluorodeoxyglucose positron emission tomography. J Nucl Cardiol 2005; 12: 294-301.

[10] Abdelbaky A, Corsini E, Figueroa AL, Fontanez S, Subramanian S, Ferencik M, Brady TJ, Hoffmann U and Tawakol A. Focal Arterial Inflammation Precedes Subsequent Calcification in the Same Location: A Longitudinal FDG-PET/CT Study. Circ Cardiovasc Imaging 2013; 6: 747-754.

[11] Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, Healey LA, Kaplan SR, Liang MH, Luthra HS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988; 31: 315-324.

[12] Bural GG, Torigian DA, Chamroonrat W, Houseni M, Chen W, Basu S, Kumar R and Alavi A. FDG-PET is an effective imaging modality to detect and quantify age-related atherosclerosis in large arteries. Eur J Nucl Med Mol Imaging 2008; 35: 562-569.

[13] del Rincon ID, Williams K, Stern MP, Freeman GL and 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.

[14] Rominger A, Saam T, Wolpers S, Cyran CC, Schmidt M, Foerster S, Nikolaou K, Reiser MF, Bartenstein P and Hacker M. 18F-FDG PET/CT identifies patients at risk for future vascular events in an otherwise asymptomatic cohort with neoplastic disease. J Nucl Med 2009; 50: 1611-1620.

[15] Paulmier B, Duet M, Khayat R, Pierquet-Ghazzar N, Laissy JP, Maunoury C, Hugonnet F, Sauvaget E, Trinquart L and Faraggi M. Arterial wall uptake of fluorodeoxyglucose on PET imaging in stable cancer disease patients indicates higher risk for cardiovascular events. J Nucl Cardiol 2008; 15: 209-217.

[16] Aziz K, Berger K, Claycombe K, Huang R, Patel R and Abela GS. Noninvasive detection and localization of vulnerable plaque and arterial thrombosis with computed tomography angiography/positron emission tomography. Circulation 2008; 117: 2061-2070.

[17] Fayad ZA, Mani V, Woodward M, Kallend D, Abt M, Burgess T, Fuster V, Ballantyne CM, Stein EA, Tardif JC, Rudd JH, Farkouh ME and Tawakol A. Safety and efficacy of dalcetrapib on atherosclerotic disease using novel non-invasive multimodality imaging (dal-PLAQUE): a randomised clinical trial. Lancet 2011; 378: 1547-1559.