Am J Cardiovasc Dis 2012;2(4):285-292
www.AJCD.us /ISSN:2160-200X/AJCD1206005

Original Article

Aortic vascular inflammation in psoriasis is associated with HDL particle size and concentration: a pilot study

YiDing Yu[1], Nikhil Sheth[1], Parasuram Krishnamoorthy[1], Babak Saboury[2], Anna Raper[1], Amanda Baer[1], Rachel Ochotony[1], Julia Doveikis[1], Stephanie DerOhannessian[1], Abby S Van Voorhees[3], Drew A Torigian[2], Abass Alavi[2], Joel M Gelfand[3,4,5], Nehal N Mehta[1,5,6]

[1]Cardiovascular Institute, University of Pennsylvania, 6 Penn Tower, Philadelphia, Pennsylvania, USA; [2]Department of Radiology, University of Pennsylvania, 3400 Spruce St., Philadelphia, Pennsylvania, USA; [3]Department of Dermatology, University of Pennsylvania, 14 Penn Tower, Philadelphia, Pennsylvania, USA; [4]Department of Epidemiology and Biostatistics, University of Pennsylvania, 8 Blockley Hall, Philadelphia, Pennsylvania, USA; [5]Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania, 8 Blockley Hall, Philadelphia, Pennsylvania, USA; [6]National Heart, Lung, and Blood Institute, Bethesda, Maryland, USA.

Received June 22, 2012; accepted September 9, 2012; Epub October 23, 2012; Published November 15, 2012

Abstract: Psoriasis is a model Th1-mediated inflammatory disease associated with increased incidence of stroke and cardiovascular disease (CVD). The mechanism behind these associations is unknown, however abnormal HDL particle composition measured by nuclear magnetic resonance (NMR) spectroscopy has been shown to be associated with CVD. Using [18F]-fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET/CT), a validated surrogate marker of CVD, we assessed whether HDL particle size and concentration were associated with vascular inflammation in patients with psoriasis. Patients with psoriasis were prospectively enrolled (439 aortic samples from 10 patients). Lipoprotein profiles using NMR spectroscopy were obtained and the relationship between vascular inflammation within the thoracic aorta by FDG-PET/CT was analyzed for association with lipoprotein particle characteristics. The plasma total cholesterol (206 mg/dL (IQR 154-229)), LDL (105 (90-161)), and triglyceride levels were within normal range (151 (94-191)) while HDL levels were low (28.9 (27.2-31.3)); however, the NMR profile demonstrated an atherogenic profile with increased small LDL and HDL particles. Total HDL particle concentration ($p<0.001$) and HDL particle size ($p<0.001$) were associated with decreased aortic inflammation, while concentration of small HDL particles was associated with increased inflammation ($p<0.001$). The association of total HDL particle concentration (β -0.0113, $p=0.002$) and small HDL particle concentration (β 0.026, $p<0.001$) with aortic inflammation persisted following adjustment for CVD risk factors. Total HDL particle concentration and small HDL particle concentration were associated with vascular inflammation within the thoracic aorta in psoriasis. These findings suggest that HDL particle characteristics may play an important role in psoriatic vascular inflammation and CVD.

Keywords: Psoriasis, inflammation, atherosclerosis, high-density lipoprotein cholesterol particle, FDG PET CT

Introduction

Recently, [18F]-fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET/CT) has emerged as a promising biomarker for the measurement of *in vivo* vascular inflammation [1]. Used in clinical studies as a surrogate marker for macrophage activity, FDG-PET/CT localizes and measures active inflammation within vessel walls, a specificity that allows FDG-PET to capture dynamic inflammatory changes [2, 3]. Indeed, vascular inflammation on FDG-PET/CT has been associated with aging [4], adverse carotid events [2, 5], aortic dissection [6], and elevated hs-CRP [7, 8], while clinical trials of statin therapy [9, 10] and lifestyle modification [11] have demonstrated reductions in vascular inflammation.

These studies suggest that FDG-PET/CT may have a promising role in advancing our understanding of atherosclerosis and vascular inflammation, particularly in settings of dynamic chronic inflammation. Using FDG-PET/CT, our

group recently demonstrated that patients with moderate to severe psoriasis have greater inflammation in the aorta compared to healthy controls, an observation that persisted after adjustment for cardiovascular risk factors, including low-density lipoprotein (LDL) and high-density lipoprotein (HDL) levels [12]. Psoriasis is a chronic T-helper (Th) 1/17-mediated inflammatory skin disease that affects approximately 2-3% of the U.S. population and over 125 million people worldwide. Patients with severe disease demonstrate an increased risk of stroke, myocardial infarction, and cardiovascular mortality, and psoriasis has recently been identified as an emerging cardiovascular risk factor [13-17]. Therefore, psoriasis provides a unique disease state in which the impact of chronic in vivo inflammation can be examined on cardiometabolic diseases such as atherosclerosis and lipoprotein metabolism.

A growing body of literature suggests that chronic inflammatory states such as psoriasis may adversely affect lipoprotein metabolism, and predispose to high density lipoprotein (HDL) dysfunction through the production of proinflammatory lipoprotein particles and the impairment of reverse cholesterol transport [18-20]. Other chronic inflammatory states, including type 2 diabetes mellitus and insulin resistance, alter lipoprotein composition, resulting in proatherogenic changes characterized by an increase in small LDL or HDL particles and a decrease in large lipoprotein particles [21]. These variations in lipoprotein particle size add a dimension to our understanding of lipoprotein function not captured by traditional measurements of LDL and HDL cholesterol concentrations. In large-scale population studies, lipoprotein particle size and concentration have been observed to associate with cardiovascular events independent of traditional lipoprotein levels, suggesting that measurement of lipoprotein particles may yield new insights into the relationship between inflammation and atherosclerosis [22-25].

Variations in lipoprotein particle size and concentration may therefore have measurable effects on vascular inflammation observed on FDG-PET/CT, and such relationships may offer promising insight into inflammatory drivers of cardiovascular risk. To study the relationship between lipoprotein particle variation and vascular inflammation, we performed a proof-of-concept pilot study using psoriasis a model system for chronic inflammation [26]. Using FDG-PET/CT, we investigated whether vascular inflammation measured within the thoracic aorta, a clinically significant risk factor for stroke, myocardial infarction and aneurysm rupture, was associated with HDL particle size and concentration in the setting of chronic psoriasis.

Materials and methods

Subjects and study design

We prospectively enrolled patients ages 18 to 70 with psoriasis (n=10) involving a body surface area (BSA) >10%. We excluded individuals with diabetes mellitus, history of cardiovascular disease, uncontrolled hypertension (defined as systolic blood pressure >180 mmHg or diastolic blood pressure >95 mmHg), pregnancy or lactation, regular use of alcoholic beverages (>2 drinks per day), major systemic or psychiatric disease, recent invasive surgery, or recent participation in interventional drug trials. Patients were recruited from dermatology and preventive cardiology clinics at the University of Pennsylvania. The study complied with the Declaration of Helsinki and was approved by the Institutional Review Board of the University of Pennsylvania. All subjects provided written informed consent.

Research protocol

Patients fasted 8 hours prior to the study and volunteered blood samples for the measurement of fasting glucose, high sensitivity C-reactive protein (hs-CRP), erythrocyte sedimentation rate (ESR), and lipid profile. Lipoprotein particle size and concentration were determined by nuclear magnetic resonance (NMR) spectroscopy (Liposcience, Raleigh, NC) as previously described [22]. Patients then underwent a whole body FDG-PET/CT scan as previously described (Gemini TF, Philips Medical Systems) [12] and PET/CT image acquisition commenced ~60 minutes after intravenous administration of ~140 μCi/kg FDG to maximize detection of macrophage activity. Axial, sagittal, and coronal PET reconstructions were interpreted with attenuation correction using CT images for attenuation correction and anatomical correlation. 2D circular regions of interests (ROI) were manually placed on each PET slice image around the external contour of the thoracic

aorta (total n=439). Mean standardized uptake values (SUV) and areas of each ROI were measured for each slice using dedicated PET/CT image analysis software (Extended Brilliance Workstation, Philips Healthcare, Bothell, WA). To correct mean SUV values for background blood activity, we divided the mean SUV per slice by the average blood SUV estimated from the inferior vena cava below the level of the renal arteries [27]. This produced a background-corrected SUV known as arterial tissue-to-background ratio (TBR), a widely utilized measure of vascular inflammation [28].

Statistical analysis

The primary outcome of this study was vascular inflammation within the thoracic aorta, measured as TBR in 439 FDG PET samples. The unadjusted association of cardiovascular risk factors and lipoprotein particle characteristics with vascular inflammation was assessed using Spearman's correlation (ρ). Multivariate linear regression was used to describe the association of HDL particle concentration with aortic inflammation after adjustment of traditional cardiovascular risk factors. Because vascular inflammation values within a subject may be highly correlated, we further performed random effects and fixed effects regression models to adjust for within subject correlation of TBR among FDG PET samples and present the results of the fixed effect model. All analyses were performed in STATA 11 [StataCorp, College Station, Texas].

Results

Subject characteristics

Subject characteristics are summarized in **Table 1**. Briefly, 80% of study participants were male, the median age was 49 (Interquartile range (IQR) 42-53) and the median body surface area affected by psoriasis was 19% (13-32). Among study participants, 1 patient reported biologic use within the last 3 months, 2 patients reported methotrexate use only, 6 patients used topical steroids only, and 1 patient was untreated. Subjects were obese (body mass index (BMI) 31 (28-37)) and had normal hs-CRP (2.7 (1.95-10.7) mg/L), blood pressure (systolic 130 (112-137) mmHg) and fasting glucose (87 (79-92) mg/dl) with mostly normal fasting lipid parameters. Strikingly, NMR spectroscopy of lipoprotein particles revealed an atherogenic lipoprotein profile similar to that seen in insulin resistant individuals [21], characterized by lower concentrations of large LDL particles, higher concentrations of small LDL and small HDL particles, and decreased average LDL and HDL particle size.

Thoracic aortic inflammation

A total of 439 thoracic aorta samples were identified and measured by FDG-PET/CT. The mean inflammation in the thoracic aorta as measured by TBR was 1.25 (SD 0.22). Medication use, including use of biologics (n=1), methotrexate (n=2), and topic steroids (n=6) demonstrated no correlation with inflammation in the thoracic aorta by Spearman correlation. In this limited age range, we found that age was negatively correlated with aortic inflammation in univariate analysis. Other known cardiovascular risk factors including gender, BMI, serum triglycerides, total cholesterol, LDL cholesterol, and HDL cholesterol demonstrated expected relationships with vascular inflammation (**Table 2**). There was no statistically significant relationship observed between aortic inflammation and hs-CRP, a commonly used biomarker for inflammation. However, proatherogenic lipoprotein particles, namely total LDL particle concentration (Spearman's ρ 0.43, p<0.001), small LDL particle concentration (ρ 0.23, p<0.001), and small HDL particle concentration (ρ 0.24, p<0.001), were associated with increased aortic inflammation. In contrast, cardioprotective lipoprotein profiles such as total HDL particle concentration (ρ -0.16, p<0.001), large HDL particle concentration (ρ -0.59, p<0.001), and HDL size (ρ -0.64, p<0.001) were correlated with lower levels of vascular inflammation.

To test whether these associations remained robust after adjustment for traditional cardiovascular risk factors, we used multivariate analysis fitted using fixed effects and random effects models to accommodate for within subject correlation of thoracic aorta SUV. The association of both total HDL particle concentration (β -0.013, p<0.001) and small HDL particle concentration (β 0.026, p<0.001) with thoracic aorta inflammation remained robust in our model adjusted for age (β 0.058, p<0.001), male gender (β 0.408, p<0.001), systolic blood pressure (β 0.012, p<0.001), LDL cholesterol (β 0.014, p<0.001), and HDL cholesterol (β -

Table 1. Study subject characteristics

Variable	Sample Characteristics* N=10
Age	49 (42-53)
Male, count (%)	8 (80%)
Body Surface Area	19 (13-32)%
PGA†	3 (2.3-3.3)
PASI	11.1 (9.2-17.2)
Body Mass Index	31 (28-37)
Waist-hip ratio	1.0 (0.85-1.0)
Fasting glucose (mg/dl)	87 (79-92)
Systolic blood pressure (mmHg)	130 (112-137)
Diastolic blood pressure (mmHg)	79 (71-84)
Hypertension, count (%)	2 (20%)
Antihypertensive, count (%)	1 (10%)
Tobacco, count (%)	2 (20%)
Statin, count (%)	2 (25%)
hs-CRP, mg/L	2.7 (1.95-10.7)
Erythrocyte sedimentation rate	12 (5-22.5)
Serum Total Cholesterol (mg/dl)	206 (154-229)
Serum Triglycerides (mg/dl)	151 (94-191)
Serum HDL cholesterol (mg/dl)	38 (36-39)
Serum LDL cholesterol (mg/dl)	105 (90-161)
LDL particle concentration (nmol/l)	1341 (940-1746)
Large LDL particle concentration (nmol/l)	218 (100-345)
Small LDL particle concentration (nmol/l)	1148 (695-1533)
LDL size (nm)	20.2 (19.7-20.4)
HDL particle concentration (μmol/l)	28.9 (27.2-31.3)
Large HDL particle concentration (μmol/l)	4.2 (3.1-5.3)
Small HDL particle concentration (μmol/l)	22.2 (14.8-25.4)
HDL size (nm)	8.7 (8.5-8.9)

*Values represent median (IQR) unless otherwise specified. †The body surface area, Physician Global Assessment (PGA), and Psoriasis Area and Severity Index (PASI) are measures of degree and severity of psoriasis disease.

0.006, $p<0.001$).

Discussion

The role of HDL cholesterol in the setting of chronic inflammation has garnered significant attention in recent years. HDL cholesterol is a key anti-inflammatory molecule credited with potent cardioprotective effects [23]. The antiatherogenic effects of HDL cholesterol are largely attributed to its role in reverse cholesterol transport, but HDL cholesterol is composed of a complex array of HDL particles, which vary substantially in size and function between individuals [29]. Traditionally, HDL cholesterol levels are measured in serum and considered a single entity, but emerging evidence suggests that higher HDL cholesterol concentration is not universally protective against cardiovascular events [30].

Indeed, proatherogenic HDL cholesterol has been described in both mouse and human studies, and has been proposed to occur in settings of chronic systemic inflammation, resulting in proinflammatory HDL particles and reduced cholesterol efflux [20]. A similar chronic inflammatory environment is observed in psoriasis [26] and postulated to contribute to the increased incidence of aortic inflammation,

Table 2. Unadjusted associations with thoracic aorta vascular inflammation.

Variables	Spearman's correlation coefficient (ρ) on Thoracic Aorta Inflammation, TBR* n = 439 aortic slices	P-value
Age	-0.49	<0.001
Male	0.36	<0.001
Body Mass Index	0.12	0.014
hs-CRP	-0.20	0.40
Serum Triglycerides (mg/dl)	0.23	<0.001
Serum Total Cholesterol (mg/dl)	0.35	<0.001
Serum LDL Cholesterol (mg/dl)	0.40	<0.001
Serum HDL Cholesterol (mg/dl)	-0.42	<0.001
LDL particle concentration (mmol/l)	0.43	<0.001
Large LDL particle concentration (nmol/l)	0.04	0.40
Small LDL particle concentration (nmol/l)	0.23	<0.001
LDL size (nm)	-0.12	0.01
HDL particle concentration (μmol/l)	-0.16	<0.001
Large HDL particle concentration (μmol/l)	-0.59	<0.001
Small HDL particle concentration (μmol/l)	0.24	<0.001
HDL size (nm)	-0.64	<0.001

*TBR- Tissue to background ratio.

stroke, and myocardial infarction seen in this patient population [12-14]. Specifically, the chronic activation of Th-1/17 pathways in psoriasis in thought to be a major driver for cardiovascular risk and serves as a model for studying the relationship between inflammation and atherogenesis [26].

Using FDG PET/CT to measure in vivo vascular inflammation as a surrogate for vascular disease [2, 31], we demonstrate in this study that abnormalities in lipoprotein particle size and number, namely decreased concentration of total HDL particles and large HDL particles and increased concentration of small LDL and HDL particles, are associated with aortic inflammation in patients with psoriasis. Among these, the association of total HDL particle concentration and small HDL particles with vascular inflammation remained robust after multivariate analysis adjusting for traditional cardiovascular risk factors, including age, gender, blood pressure, and LDL and HDL cholesterol. This suggests that cellular dysfunction associated with the pathogenesis of psoriasis via T-cells, macrophages and dendritic cells may contribute to the accelerated vascular diseases observed in psoriasis.

While epidemiology studies measuring HDL particle profiles remain limited, these findings are consistent with existing studies linking HDL particle abnormalities with cardiovascular disease. Small HDL particles are associated with increased coronary atherosclerosis [32] while combined niacin and statin therapy [33] promotes an increase in both total HDL particle concentration and HDL particle size. Studies that have examined cardiovascular outcomes further suggest a role for HDL particle measurements in cardiovascular risk prediction. The Veterans Affairs High-Density Lipoprotein Intervention Trial substudy was the first major prospective study to investigate the role of HDL particles in coronary artery disease, finding that total HDL particle concentration was associated with new coronary artery disease events independent of traditional cardiovascular risk factors [34]. Similar results were reported by the EPIC (European Prospective Investigation into Cancer and Nutrition)-Norfolk study, which found that patients with higher total HDL particle concentration and larger HDL particle size had lower risk of first coronary artery event after adjustment for traditional cardiovascular risk factors [23], findings concordant with our observation that large HDL particles were associated with lower vascular inflammation within the aorta.

Taken together, the results seen in this body of literature suggest that concentration and size of HDL particles may have unique effects on atherogenesis, though the mechanism remains unknown. In this pilot study, we set out to de-

scribe the association of HDL particle concentration and size with *in vivo* vascular inflammation using a novel application of FDG-PET/CT. Our results demonstrate that FDG-PET/CT can be used to describe the effects of HDL particle concentration and size on vascular inflammation in the setting of chronic inflammation. In particular, we found that higher concentrations of total HDL particles and larger HDL size are associated with lower levels of aortic inflammation, suggesting that greater concentrations of HDL particles, and large HDL particles in particular, convey greater anti-inflammatory capacity, while the converse may true for small HDL particles [29]. Overall, these findings suggest that variations in HDL particle concentration and size correlate with the degree of aortic vascular inflammation in patients with psoriasis, and may provide potential mechanistic insight linking psoriasis and cardiovascular disease.

Several limitations of this study are important to consider. First, this study is cross sectional, and therefore unable to test causal relationships. Additionally, while Th-1 activation in psoriasis shares many pathways with atherogenesis, inflammation observed in psoriasis may not be generalizable to other populations. We found that age was inversely correlated with vascular inflammation in univariate analysis, a result that may reflect the narrow age range in the study sample as our prior study noted an increase in vascular inflammation with aging [4]. Furthermore, in multivariate analysis, increasing age demonstrated a strong correlation with vascular inflammation after inclusion of other cardiovascular risk factors such as gender, BMI, and dyslipidemia, all of which demonstrated expected relationships with aortic inflammation. In addition, while our study is similar in size to other prospective FDG PET/CT studies, additional studies are certainly needed to replicate and extend our findings in a larger population. Nonetheless, this proof-of-concept study demonstrates that subtle variations in vascular inflammation can be captured by FDG PET/CT which can then be used to study novel relationships between vascular inflammation and emerging risk factors. Future studies examining exposure to psoriasis in either a case-control or prospective cohort study will be necessary to elucidate the mechanistic role of psoriasis in HDL dysfunction and atherogenesis.

In conclusion, among patients with severe psoriasis, vascular inflammation of the thoracic aorta assessed by FDG PET/CT was inversely associated with large HDL particle concentration and HDL particle size, and independently associated with total HDL and small HDL particle concentrations. Our findings suggest that HDL particle size may reveal underlying differences in the composition and function of HDL, and correlate with vascular inflammation in psoriasis. Future studies are needed to replicate these findings in a larger population, to examine if vascular inflammation measured by FDG-PET/CT correlate with HDL lipoprotein particle characteristics over time, and to investigate the mechanistic effect, if any, of chronic psoriasis on HDL function and vascular inflammation.

Sources of funding

This study was supported in part by a grant from the Doris Duke Charitable Foundation (YY), by a grant from the National Psoriasis Foundation (NNM), by K23HL097151-01 (NNM), 1P30 ES013508-05 from the National Institute of Environmental Health Sciences, NIH (DAT), NHLBI RO1HL089744 (JMG), and P50 HL-083799-SCCOR (Penn).

Role of sponsors

The sponsors had no role in the design and conduct of the study; in the collection, analysis, and interpretation of data; or in the preparation, review, or approval of the manuscript.

Disclosures of all financial interests (including pharmaceutical and device products)

Employment: none. Consultancies: Gelfand – Amgen, Pfizer, Novartis, Centocor, Celgene, Abbott, Van Voorhees – Amgen, Abbott, Genentech, Incyte, Warner Chilcott, Connetics, Bristol Myers Squibb, IDEC, Centocor, VGX, Xtrc, Leo. Honoraria: Van Voorhees – Amgen, Abbott, Genentech, Incyte, Warner Chilcott, Connetics, Bristol Myers Squibb, IDEC, Centocor, VGX, Xtrc, Leo. Speakers bureau: none. Stock ownership or options: Van Vorhees – Merck, Torigian – Pfizer. Expert testimony: none. Grants: Gelfand – Amgen, Abbott, Novartis, Pfizer; Torigian – Pfizer, Van Voorhees – Amgen, Astellas, Bristol Myers Squibb, Roche. Patents filed, received, pending, or in preparation: none. Royalties: none. Donation of medical equipment: none.

Address correspondence to: Chief, Section of Inflammation and Cardiometabolic Diseases, National

Heart, Lung and Blood Institute, Bethesda, MD 20892, USA. Tel: 301-827 0483; Fax: 301-451 7093; E-mail: nehal.mehta@nih.gov

References

[1] Rudd JH, Narula J, Strauss HW, Virmani R, Machac J, Klimas M, Tahara N, Fuster V, Warburton EA, Fayad ZA and Tawakol AA. Imaging atherosclerotic plaque inflammation by fluorodeoxyglucose with positron emission tomography: ready for prime time? J Am Coll Cardiol 2010; 55: 2527-2535.

[2] Tawakol A, Migrino RQ, Bashian GG, Bedri S, Vermylen D, Cury RC, Yates D, LaMuraglia GM, Furie K, Houser S, Gewirtz H, Muller JE, Brady TJ and Fischman AJ. In vivo 18F-fluorodeoxyglucose positron emission tomography imaging provides a noninvasive measure of carotid plaque inflammation in patients. J Am Coll Cardiol 2006; 48: 1818-1824.

[3] 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.

[4] 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.

[5] Moustafa RR, Izquierdo-Garcia D, Fryer TD, Graves MJ, Rudd JH, Gillard JH, Weissberg PL, Baron JC and Warburton EA. Carotid plaque inflammation is associated with cerebral microembolism in patients with recent transient ischemic attack or stroke: a pilot study. Circ Cardiovasc Imaging 2010; 3: 536-541.

[6] Kato K, Nishio A, Kato N, Usami H, Fujimaki T and Murohara T. Uptake of 18F-FDG in acute aortic dissection: a determinant of unfavorable outcome. J Nucl Med 2010; 51: 674-681.

[7] Yang SJ, Kim S, Choi HY, Kim TN, Yoo HJ, Seo JA, Kim SG, Kim NH, Baik SH, Choi DS and Choi KM. High-sensitivity C-reactive protein in the low- and intermediate-Framingham risk score groups: Analysis with (18)F-fluorodeoxyglucose positron emission tomography. Int J Cardiol 2011.

[8] Yoo HJ, Kim S, Park MS, Yang SJ, Kim TN, Seo JA, Kim SG, Kim NH, Seo HS, Baik SH, Choi DS and Choi KM. Vascular inflammation stratified by C-reactive protein and low-density lipoprotein cholesterol levels: analysis with 18F-FDG PET. J Nucl Med 2011; 52: 10-17.

[9] Ishii H, Nishio M, Takahashi H, Aoyama T, Tanaka M, Toriyama T, Tamaki T, Yoshikawa D, Hayashi M, Amano T, Matsubara T and Murohara T. Comparison of atorvastatin 5 and 20 mg/d for reducing F-18 fluorodeoxyglucose uptake in atherosclerotic plaques on positron emission tomography/computed tomography: a randomized, investigator-blinded, open-label, 6-month study in Japanese adults scheduled for percutaneous coronary intervention. Clin Ther 2010; 32: 2337-2347.

[10] Tahara N, Kai H, Ishibashi M, Nakaura H, Kaida H, Baba K, Hayabuchi N and Imaizumi T. Simvastatin attenuates plaque inflammation: evaluation by fluorodeoxyglucose positron emission tomography. J Am Coll Cardiol 2006; 48: 1825-1831.

[11] Lee SJ, On YK, Lee EJ, Choi JY, Kim BT and Lee KH. Reversal of vascular 18F-FDG uptake with plasma high-density lipoprotein elevation by atherogenic risk reduction. J Nucl Med 2008; 49: 1277-1282.

[12] 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.

[13] Gelfand JM, Dommasch ED, Shin DB, Azfar RS, Kurd SK, Wang X and Troxel AB. The risk of stroke in patients with psoriasis. J Invest Dermatol 2009; 129: 2411-2418.

[14] 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.

[15] Mehta NN, Azfar RS, Shin DB, Neimann AL, Troxel AB and Gelfand JM. Patients with severe psoriasis are at increased risk of cardiovascular mortality: cohort study using the General Practice Research Database. Eur Heart J 2010; 31: 1000-1006.

[16] Mehta NN, Yu Y, Pinnelas R, Krishnamoorthy P, Shin DB, Troxel AB and Gelfand JM. Attributable risk estimate of severe psoriasis on major cardiovascular events. Am J Med 2011; 124: 775 e771-776.

[17] Friedewald VE, Cather JC, Gelfand JM, Gordon KB, Gibbons GH, Grundy SM, Jarratt MT, Krueger JG, Ridker PM, Stone N and Roberts WC. AJC editor's consensus: psoriasis and coronary artery disease. Am J Cardiol 2008; 102: 1631-1643.

[18] de la Llera Moya M, McGillicuddy FC, Hinkle CC, Byrne M, Joshi MR, Nguyen V, Tabita-Martinez J, Wolfe ML, Badellino K, Pruscino L, Mehta NN, Asztalos BF and Reilly MP. Inflammation modulates human HDL composition and function in vivo. Atherosclerosis 2012; 222: 390-394.

[19] Navab M, Anantharamaiah GM, Reddy ST, Van Lenten BJ, Ansell BJ and Fogelman AM. Mechanisms of disease: proatherogenic HDL--an evolving field. Nat Clin Pract Endocrinol Metab

2006; 2: 504-511.
[20] McGillicuddy FC, de la Llera Moya M, Hinkle CC, Joshi MR, Chiquoine EH, Billheimer JT, Rothblat GH and Reilly MP. Inflammation impairs reverse cholesterol transport in vivo. Circulation 2009; 119: 1135-1145.
[21] Garvey WT, Kwon S, Zheng D, Shaughnessy S, Wallace P, Hutto A, Pugh K, Jenkins AJ, Klein RL and Liao Y. Effects of insulin resistance and type 2 diabetes on lipoprotein subclass particle size and concentration determined by nuclear magnetic resonance. Diabetes 2003; 52: 453-462.
[22] Mora S, Szklo M, Otvos JD, Greenland P, Psaty BM, Goff DC, Jr., O'Leary DH, Saad MF, Tsai MY and Sharrett AR. LDL particle subclasses, LDL particle size, and carotid atherosclerosis in the Multi-Ethnic Study of Atherosclerosis (MESA). Atherosclerosis 2007; 192: 211-217.
[23] El Harchaoui K, Arsenault BJ, Franssen R, Despres JP, Hovingh GK, Stroes ES, Otvos JD, Wareham NJ, Kastelein JJ, Khaw KT and Boekholdt SM. High-density lipoprotein particle size and concentration and coronary risk. Ann Intern Med 2009; 150: 84-93.
[24] Cromwell WC, Otvos JD, Keyes MJ, Pencina MJ, Sullivan L, Vasan RS, Wilson PW and D'Agostino RB. LDL Particle Number and Risk of Future Cardiovascular Disease in the Framingham Offspring Study - Implications for LDL Management. J Clin Lipidol 2007; 1: 583-592.
[25] Blake GJ, Otvos JD, Rifai N and Ridker PM. Low-density lipoprotein particle concentration and size as determined by nuclear magnetic resonance spectroscopy as predictors of cardiovascular disease in women. Circulation 2002; 106: 1930-1937.
[26] Davidovici BB, Sattar N, Prinz JC, Puig L, Emery P, Barker JN, van de Kerkhof P, Stahle M, Nestle FO, Girolomoni G and Krueger JG. Psoriasis and systemic inflammatory diseases: potential mechanistic links between skin disease and comorbid conditions. J Invest Dermatol 2010; 130: 1785-1796.
[27] 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.
[28] Rudd JH, Myers KS, Bansilal S, Machac J, Rafique A, Farkouh M, Fuster V and Fayad ZA. (18)Fluorodeoxyglucose positron emission tomography imaging of atherosclerotic plaque inflammation is highly reproducible: implications for atherosclerosis therapy trials. J Am Coll Cardiol 2007; 50: 892-896.
[29] Watanabe H, Soderlund S, Soro-Paavonen A, Hiukka A, Leinonen E, Alagona C, Salonen R, Tuomainen TP, Ehnholm C, Jauhiainen M and Taskinen MR. Decreased high-density lipoprotein (HDL) particle size, prebeta-, and large HDL subspecies concentration in Finnish low-HDL families: relationship with intima-media thickness. Arterioscler Thromb Vasc Biol 2006; 26: 897-902.
[30] van der Steeg WA, Holme I, Boekholdt SM, Larsen ML, Lindahl C, Stroes ES, Tikkanen MJ, Wareham NJ, Faergeman O, Olsson AG, Pedersen TR, Khaw KT and Kastelein JJ. High-density lipoprotein cholesterol, high-density lipoprotein particle size, and apolipoprotein A-I: significance for cardiovascular risk: the IDEAL and EPIC-Norfolk studies. J Am Coll Cardiol 2008; 51: 634-642.
[31] 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.
[32] Freedman DS, Otvos JD, Jeyarajah EJ, Barboriak JJ, Anderson AJ and Walker JA. Relation of lipoprotein subclasses as measured by proton nuclear magnetic resonance spectroscopy to coronary artery disease. Arterioscler Thromb Vasc Biol 1998; 18: 1046-1053.
[33] Toth PP, Thakker KM, Jiang P and Padley RJ. Niacin extended-release/simvastatin combination therapy produces larger favorable changes in high-density lipoprotein particles than atorvastatin monotherapy. Vasc Health Risk Manag 2012; 8: 39-44.
[34] Otvos JD, Collins D, Freedman DS, Shalaurova I, Schaefer EJ, McNamara JR, Bloomfield HE and Robins SJ. Low-density lipoprotein and high-density lipoprotein particle subclasses predict coronary events and are favorably changed by gemfibrozil therapy in the Veterans Affairs High-Density Lipoprotein Intervention Trial. Circulation 2006; 113: 1556-1563.