Subclinical Liver Disease is Associated with Subclinical Atherosclerosis in Psoriasis: Results from Two Observational Studies

Journal:	*Journal of Investigative Dermatology*
Manuscript ID	JID-2021-0160.R1
Article Type:	Original Article
Date Submitted by the Author:	15-Apr-2021
Complete List of Authors:	Gonzalez Cantero, Alvaro; Hospital Ramon y Cajal, Department of Dermatology Teklu, Meron; National Institutes of Health, National Heart, Lung, and Blood Institute Sorokin, Alexander; National Institutes of Health, National Heart, Lung, and Blood Institute Prussick, Ronald; The George Washington University School of Medicine and Health Sciences, Department of Dermatology González Cantero, Jorge Luis; Hospital General Universitario Gregorio Marañón, Radiology Martin-Rodriguez, Jose ; University Hospital San Cecilio, Department of Radiology Patel, Nidhi; National Institutes of Health, National Heart, Lung, and Blood Institute Parel, Philip ; National Institutes of Health, National Heart, Lung, and Blood Institute Manyak, Grigory; National Institutes of Health, National Heart, Lung, and Blood Institute Teague, Heather; National Institutes of Health, National Heart, Lung, and Blood Institute Rodante, Justin; National Institutes of Health, National Heart, Lung, and Blood Institute Keel, Andrew; National Institutes of Health, National Heart, Lung, and Blood Institute Pérez-Hortet, Cristina; Complejo Hospitalario de Toledo, Department of Dermatology Sánchez-Moya, Ana Isabel; Complejo Hospitalario de Toledo, Department of Dermatology Jiménez Gómez, Natalia; Hospital Ramon y Cajal, Department of Dermatology Ballester, Maria Asuncion ; Hospital Ramon y Cajal, Department of Dermatology Solis, Jorge; Hospital Universitario Doce de Octubre, Department of Cardiology Fernandez-Friera, Leticia; Centro Integral de Enfermedades Cardiovasculares HM CIEC, HM Hospitales Barderas, Maria G.; Hospital Nacional de Paraplejicos, Department of Vascular Physiopathology

	Gonzalez-Calvin, Jorge Luis; Hospital Universitario San Cecilio, Department of Gastroenterology Jaen, Pedro; Hospital Ramon y Cajal, Department of Dermatology Playford, Martin; National Institutes of Health, National Heart, Lung, and Blood Institute Dey, Amit; National Institutes of Health, National Heart, Lung, and Blood Institute Gelfand, Joel; University of Pennsylvania Perelman School of Medicine, Department of Biostatistics; University of Pennsylvania Perelman School of Medicine, Department of Dermatology Mehta, Nehal; National Institutes of Health, National Heart, Lung, and Blood Institute
Keywords:	

Subclinical Liver Disease is Associated with Subclinical Atherosclerosis in Psoriasis: Results from Two Observational Studies

Brief title: Liver disease and atherosclerosis

Alvaro Gonzalez-Cantero, MD PhD[1*], Meron Teklu, BA[2*], Alexander V Sorokin, MD PhD[2], Ronald Prussick, MD FRCPC[3], Jorge González-Cantero, MD PhD[4], Jose Luis Martin-Rodriguez, MD[5], Nidhi Patel, BS[2], Philip M Parel [2], Grigory A Manyak, BA[2], Heather L Teague, PhD[2], Justin A Rodante, PA-C[2], Andrew Keel, CRNP[2], Cristina Pérez-Hortet, MD[6], Ana I Sanchéz-Moya, MD PhD[6], Natalia Jiménez, MD[1], Asunción Ballester, MD[1], Jorge Solis, MD, PhD[7], Leticia Fernandez-Friera, MD PhD[8], María G Barderas PhD[9], Jorge L Gonzalez-Calvin, MD PhD[10], Pedro Jaen, MD PhD[1], Martin P Playford, PhD[2,] Amit K Dey, MD[2], Joel M Gelfand, MD MSCE[11,12], Nehal N Mehta, MD MSCE FAHA[2**]

*** These authors contributed equally**

1. Department of Dermatology, Hospital Universitario Ramon y Cajal, Madrid, Spain
2. National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD, USA
3. Department of Dermatology, The George Washington School of Medicine and Health Sciences, Washington, DC, USA
4. Department of Radiology, Gregorio Marañon Hospital, Madrid, Spain
5. Department of Radiology, University Hospital San Cecilio, Granada, Spain
6. Department of Dermatology, Complejo Hospitalario de Toledo, Toledo, Spain.
7. Department of Cardiology, Hospital Universitario Doce de Octubre, Madrid, Spain
8. HM Hospitales-Centro Integral de Enfermedades Cardiovasculares HM CIEC, Madrid, Spain
9. Department of Vascular Physiopathology, Hospital Nacional de Parapléjicos, SESCAM, Toledo, Spain.
10. Department of Gastroenterology, University Hospital San Cecilio, Granada, Spain.
11. Department of Biostatistics, Epidemiology and Informatics, Perelman School of Medicine, Philadelphia, Pennsylvania, USA
12. Department of Dermatology, Perelman School of Medicine, Philadelphia, Pennsylvania, USA

**** Corresponding author:**
Nehal N. Mehta MD MSCE FAHA
Lasker Senior Investigator, Chief, Section of Inflammation and Cardiometabolic Diseases
National Heart, Lung and Blood Institute, National Institutes of Health
10 Center Drive, Clinical Research Center, Room 5-5140
Bethesda, MD 20892, USA
Telephone: 1-301-827-0483, Fax: 1-301-827-0915
Email: nehal.mehta@nih.gov

Locations of research: Toledo, Spain and Bethesda, Maryland, USA

Abbreviations

BMI; Body mass index
BSA; Body surface area
CCTA; Coronary computed tomography angiography
CVD; Cardiovascular disease
^{18}F-FDG; 2-[fluorine-18]fluoro-2-deoxy-D-glucose
NAFLD; Non-alcoholic fatty liver disease
NASH; Non-alcoholic steatohepatitis
PASI; Psoriasis area severity index
PET; Positron emission tomography
SHRI: Sonographic hepatorenal index
SUV; Standard uptake value

ABSTRACT

Psoriasis is associated with a higher risk of liver diseases. We investigated the impact of hepatic steatosis (European cohort) and hepatic inflammation (United States cohort) on subclinical atherosclerosis. In the European cohort (n=76 psoriasis participants and 76 controls), non-alcoholic fatty liver disease (NAFLD), assessed by the sonographic hepatorenal index (SHRI), was more prevalent in psoriasis than controls (61% vs 45%; p=.04). Psoriasis participants with NAFLD had a higher prevalence of subclinical atherosclerosis (ultrasonographic presence of plaque in femoral or carotid arteries) than psoriasis without NAFLD (61% vs 23%; p=.006) and controls with NAFLD (61% vs 32%; p<.05). SHRI was a determinant of subclinical atherosclerosis in psoriasis (OR, 3.5; p=.01). In the United States cohort, (n=162 psoriasis participants who underwent positron emission tomography and coronary CT angiography), those with high hepatic ^{18}F-FDG uptake had higher noncalcified (1.3 (0.49 mm^2) vs 1.0 (0.40 mm^2)), fibrofatty (0.23 (0.15 mm^2) vs 0.11 (0.087 mm^2)), and lipid rich necrotic core (4.3 (2.3 mm^2) vs 3.0 (1.7 mm^2)) coronary burden (all p<.001,). Hepatic ^{18}F-FDG uptake associated with noncalcified (β=0.28; p<.001), fibrofatty (β=0.49; p<.001) and lipid rich necrotic core (β=0.28; p=.003) burden. These results demonstrate the downstream cardiovascular effects of subclinical liver disease in psoriasis.

INTRODUCTION

Psoriasis is a chronic inflammatory condition associated with metabolic dysfunction, accelerated atherosclerosis and increased risk of myocardial infarction.(Aksentijevich et al., 2019, Gelfand et al., 2006) Psoriasis is associated with a higher incidence and prevalence of non-alcoholic fatty liver disease (NAFLD) than the general population and the risk of liver disease increases with body surface area affected by psoriasis.(Ogdie et al., 2018, van der Voort et al., 2014) NAFLD is a chronic low-grade inflammatory condition with well-known cardiovascular disease (CVD) risk.(Mahfood Haddad et al., 2017) NAFLD exhibits a spectrum of disease ranging from steatosis to the more aggressive necro-inflammatory non-alcoholic steatohepatitis (NASH), which can result in liver fibrosis and cirrhosis.(Stefan et al., 2019) Chronic systemic inflammation is central to psoriasis, NAFLD and atherosclerosis.(Aksentijevich et al., 2019, Prussick and Miele, 2018). Traditional cardiovascular risk factors do not adequately capture risk in states of chronic inflammation, making the study of risk accelerators like hepatic dysfunction and their impact on directly measured atherosclerosis burden of particular importance in psoriasis.(Crowson et al., 2012, Eder et al., 2014) Despite the higher risk of liver disease in psoriasis, there are limited data on the relationship between hepatic steatosis and atherosclerosis in patients with psoriasis.

The computerized sonographic hepatorenal index (SHRI) is a noninvasive, accurate, and validated tool for the diagnosis and quantification of liver fat. (Mancini et al., 2009, Webb et al., 2009, Xia et al., 2012) Similarly, positron emission tomography (PET) is an emerging valuable tool within inflammatory conditions. (Glaudemans et al., 2013, Mehta et al., 2011) Maximum hepatic 2-[fluorine-18]fluoro-2-deoxy-D-glucose (^{18}F-FDG) has been shown to represent irreversible uptake within inflammatory cells in the liver and therefore may be utilized as an

indicator of true hepatic inflammation.(Keramida et al., 2014) Hepatic inflammation is associated with systemic metabolic consequences and progression of NAFLD to steatohepatitis and fibrosis.(Chen et al., 2017, Gao and Tsukamoto, 2016, Gehrke and Schattenberg, 2020)

Ultrasound of vessels to identify plaques, and use of coronary computed tomography angiography (CCTA) to assess coronary atherosclerosis burden allow for non-invasive detection of subclinical atherosclerosis prior to the development of hard cardiovascular events.(Kolossváry et al., 2017, Noguchi et al., 2018, Steinl and Kaufmann, 2015) We hypothesized that hepatic dysfunction assessed as liver fat content or inflammation would associate with markers of subclinical atherosclerosis beyond traditional cardiovascular risk factors. We therefore conducted a two-stage study to assess the impact of liver disease on subclinical atherosclerosis in psoriasis. In part 1 (henceforth European cohort), we evaluated hepatic fat content and the presence of plaques in femoral and carotid arteries in controls and participants with psoriasis. In part 2 (henceforth United States cohort), we utilized hepatic ^{18}F-FDG uptake to assess liver inflammation and its impact on CCTA based coronary atherosclerosis burden in psoriasis.

RESULTS

European cohort

Comparison of participants with psoriasis to age, sex and BMI matched controls

The psoriasis cohort had a mean age of 45 years, was predominantly male (70%) and had an overweight body mass index (BMI) profile (29.7 (5.58 kg/m^2)). There was moderate to severe skin disease severity as measured by the psoriasis area severity index (PASI) score (12.8 (4.67)) and affected body surface area (BSA) (15.7 (9.34 %)) and an average disease duration of 18 years. When compared to healthy controls matched 1:1 for age, sex and BMI, participants with

psoriasis had higher waist circumferences (102 (13.8 cm) vs 96.7 (13.5 cm); p=.048), prevalence of dyslipidemia (34% vs 17%; p=.046), c-reactive protein (3.68 (4.11 mg/L) vs 2.04 (1.38 mg/L); p=.01), homeostatic model for assessment of insulin resistance (HOMA-IR) (4.30 (3.53) vs 2.60 (2.00); p=.005) and triglycerides (143 (88.2 mg/dL) vs 97.9 (41.3 mg/dL); p=.002). There was lower high density lipoprotein cholesterol (50.7 (13.7 mg/dL) vs 56.9 (14.1 mg/dL); p=.03) in the psoriasis cohort. Participants with psoriasis had a higher prevalence of NAFLD (61% vs 45%; p=.04) and subclinical atherosclerosis (46% vs 18%; p<.001) **(Table 1).**

Comparison of psoriasis participants with and without NAFLD

Of the 76 participants with psoriasis, 46 met criteria for NAFLD. The NAFLD absent and present groups were similar in PASI scores, BSA and disease duration. The NAFLD group had higher waist circumferences (107 (12.6 cm) vs 93.8 (11.7 cm); p<.001) and percentage of participants with low physical activity (20% vs 0%; p=.03) and dyslipidemia (46% vs 17% ; p=.04). While c-reactive protein did not differ between the two groups, the NAFLD group had higher alanine aminotransferase (33 (21 U/L) vs 18 (11 U/L); p=.002) and HOMA-IR (5.40 (4.00) vs 2.40 (0.92); p<.001). Triglycerides (174 (95.4 mg/dL) vs 95.1 (46.3 mg/dL); p<.001) and low density lipoprotein cholesterol (119 (29.9 mg/dL) vs 103 (22.4 mg/dL); p=.04) were higher and high density lipoprotein cholesterol lower (46.7 (11.3 mg/dL) vs 56.8 (15.0 mg/dL); p=.009) in the NAFLD group. The NAFLD group had a higher percentage of participants with subclinical atherosclerosis (61% vs 23%; p=.006) **(Table 2).**

Comparison of psoriasis participants and controls with NAFLD

Psoriasis participants with NAFLD had higher c-reactive protein (3.97 (3.71 mg/L) vs 1.79 (1.05 mg/L)), HOMA-IR (5.40 (4.00) vs 3.18 (2.69)) and triglycerides (174 (95.4 mg/dL) vs 104 (44.6

mg/dL)), all p<.05, when compared to controls with NAFLD. Hepatic fat content (1.84 (0.36) vs 1.66 (0.39); p<.05) and presence of subclinical atherosclerosis (61% vs 32%; p<.05) were higher in psoriasis participants with NAFLD than controls with NAFLD **(Table 3).**

United States cohort

Comparison of psoriasis participants with low and high hepatic ^{18}F-FDG uptake

The cohort had a mean age of 50 years, was predominantly male (64%) and had a high BMI profile (30.0 (6.19 kg/m^2)). There was mild to moderate skin disease severity as measured by PASI score (6.3 (3.2-11)) and BSA (5.6 (2.5-16 %)) and an average disease duration of 20 years (13). The high and low hepatic ^{18}F-FDG uptake groups were similar in PASI scores and BSA, but the high uptake group had a higher percentage of participants with psoriatic arthritis (35% vs 17%; p=.01). Disease duration was higher in the high uptake group but did not meet significance (22 (12 years) vs 18 (14 years); p=.07). The high uptake group had significantly higher proportions of men (77% vs 51%; p<.001) and participants on lipid lowering therapy (42% vs 21%; p=.004). The high uptake group had higher waist circumferences (106 (94-119 cm) vs 93 (84-102 cm); p<.001) and prevalence of metabolic syndrome (45% vs 20%; p<.001). While high sensitivity c-reactive protein did not differ between the two groups, the high uptake group had higher HOMA-IR (3.7 (2.3-5.3) vs 2.2 (1.5-3.3); p<.001), and triglycerides (110 (81-174 mg/dL) vs 92 (71-127 mg/dL); p=.04) as well as lower high density lipoprotein cholesterol (50 (40-59 mg/dL) vs 52 (46-70 mg/dL); p=.01). Those with high hepatic uptake had higher total (1.4 (0.51 mm^2) vs 1.1 (0.42 mm^2); p<.001), noncalcified (1.3 (0.49 mm^2) vs 1.0 (0.40 mm^2); p<.001), fibrofatty (0.23 (0.15 mm^2) vs 0.11 (0.087 mm^2); p<.001), fibrous (1.0 (0.37 mm^2) vs 0.90 (0.34 mm^2); p=.02), and lipid rich necrotic core (4.3 (2.3 mm^2) vs 3.0 (1.7 mm^2); p<.001) coronary

burden. Dense calcified burden was higher in those with low uptake (0.07 (0.08 mm^2) vs 0.04 (0.07 mm^2); p=.03) **(Table 4).**

Association between hepatic steatosis, hepatic inflammation and subclinical atherosclerosis

In logistic regression analysis for participants with psoriasis from the European cohort, SHRI was a significant determinant of subclinical atherosclerosis (odds ratio=5.0; 95% confidence interval: 1.2-20; p=.02). After adjusting for age, sex, current smoking, waist circumference, HOMA-IR, systolic blood pressure, high density lipoprotein cholesterol, low density lipoprotein cholesterol, triglycerides, and c-reactive protein, the relationship remained significant (odds ratio=3.5; 95% confidence interval: 1.5-24; p=.01). In controls, SHRI associated with subclinical atherosclerosis in unadjusted models (odds ratio=2.2; 95% confidence interval: 1.1-16; p=.02), but the relationship became insignificant after adjustment for the above covariates (odds ratio=1.0; 95% confidence interval: 0.7-13; p=.06) **(Table 5a)**. The maximum hepatic ^{18}F-FDG uptake significantly associated with noncalcified (β=0.48; p<.001), fibrofatty (β=0.62; p<.001), fibrous (β=0.24; p=.003) and lipid rich necrotic core (β=0.29; p<.001) coronary burden in participants with psoriasis from the United States cohort. After adjusting for the above covariates, hepatic ^{18}F-FDG uptake remained significantly associated with noncalcified (β=0.28; p<.001), fibrofatty (β=0.49; p<.001) and lipid rich necrotic core (β=0.28; p=.003) coronary burden **(Table 5b).** Adjusting for the presence of psoriatic arthritis did not affect these relationships.

DISCUSSION

In this two-stage, cross-sectional study, we showed a higher prevalence of NAFLD in psoriasis compared to controls and elevated hepatic fat content in psoriasis participants with NAFLD than

controls with NAFLD. Participants with psoriasis and NAFLD had a higher prevalence of subclinical atherosclerosis than psoriasis participants without NAFLD and controls with NAFLD. SHRI, a measure of hepatic fat content, was a significant determinant of the presence of subclinical atherosclerosis in psoriasis after adjustment for traditional cardiovascular risk factors. Interestingly, there appears to be a trend of a stronger association between hepatic fat content and subclinical atherosclerosis in psoriasis than controls. Given the importance of hepatic inflammation in NAFLD, we utilized the United States cohort to assess the association between hepatic inflammation and direct coronary atherosclerosis burden. We showed that those with high hepatic ^{18}F-FDG uptake were more metabolically deranged and had a higher burden of noncalcified, fibrofatty, fibrous and lipid rich necrotic core as assessed by CCTA. In addition, hepatic ^{18}F-FDG significantly associated with high risk coronary atherosclerosis burden in fully adjusted models. Together, these findings further demonstrate the importance of liver disease in psoriasis.

Twenty-five percent of the global population has NAFLD with continued increasing incidence.(Younossi, 2019) NAFLD and its associated metabolic derangements such as adiposity, metabolic syndrome and insulin resistance are known to be more prevalent in patients with psoriasis.(Love et al., 2011, van der Voort et al., 2014) Both NAFLD and psoriasis are associated with an increased risk of CVD, with both conditions known to accelerate atherosclerosis.(Aksentijevich et al., 2019, Kasper et al., 2020) Thus, understanding the contribution of NAFLD in psoriasis to subclinical atherosclerosis is of great importance. In this study, we showed that the presence of femoral or carotid atheromas is more prevalent in participants with psoriasis and NAFLD when compared to psoriasis without NAFLD and controls with NAFLD. Furthermore, hepatic fat content was higher in participants with psoriasis

and NAFLD when compared to controls with NAFLD and was a significant determinant of subclinical atherosclerosis independent of traditional cardiovascular risk factors in psoriasis. While the mechanistic link between NAFLD and CVD risk is complex, it is known that the consequential dyslipidemia and insulin resistance, both of which are higher in states of chronic inflammation and in our psoriasis cohort with NAFLD, play an important role.(Kasper et al., 2020) Lifestyle modifications and pharmacologic interventions have been shown to reduce the extent of NAFLD and its CVD risk.(Armstrong et al., 2016, Campanati et al., 2013, Katsagoni et al., 2017, Tikkanen et al., 2013) Given the prevalence of liver disease in psoriasis, our study provides further evidence for increased clinical vigilance for the presence and consequences of hepatic dysfunction in patients with psoriasis.

Hepatic inflammation is associated with insulin resistance, elevated lipid levels and the metabolic syndrome, all factors significantly elevated in our cohort with high hepatic ^{18}F-FDG uptake and factors important for the development and progression of NAFLD.(Chatterjee, 2010, Meshkani and Adeli, 2009, Popa et al., 2007, Senn et al., 2002) Lipid accumulation in hepatocytes can trigger localized inflammation and the resulting damage creates a feedback loop that aggravates inflammation. This phenomenon is important in the progression of NAFLD, NASH and cirrhosis and increases comorbidities associated with NAFLD.(Gehrke and Schattenberg, 2020, Koyama and Brenner, 2017) While the quantification of inflammation in the liver is complicated by the relationship between ^{18}F-FDG kinetics and hepatocyte biology, there is evidence supporting the use of the maximum standard uptake value (SUV) as a marker of true and irreversible uptake of ^{18}F-FDG in the inflammatory cells within the liver.(Keramida et al., 2014) The European cohort showed that hepatic steatosis was higher in psoriasis and associates with subclinical atherosclerosis. Results from the United States cohort buttress these findings by

showing that participants with psoriasis and high hepatic inflammation had higher levels of metabolic abnormalities and direct measures of coronary atherosclerosis burden. Of note, dense calcified burden, a more stable atherosclerosis burden subtype (van Rosendael et al., 2020), was higher in those with low hepatic uptake. Furthermore, ^{18}F-FDG significantly associated with high risk atherosclerosis features such as noncalcified and lipid rich necrotic core burden independent of traditional cardiovascular risk factors. Taken together, these findings further highlight the higher prevalence of liver disease in psoriasis and the high risk atherosclerosis phenotypes associated with markers of liver disease in psoriasis. In the clinical setting, heightened awareness of the presence and consequences of hepatic dysfunction is warranted amongst patients and providers.

The main limitations of this study are its cross-sectional nature and relatively small sample size which limit ability to establish causality and directionality. While we illustrate an association between subclinical liver dysfunction and atherosclerosis, larger studies designed to establish causality are needed to better understand this relationship in psoriasis. Larger studies are also needed to confirm the trend towards a stronger association between SHRI and subclinical atherosclerosis in psoriasis compared to controls.

In conclusion, we showed that participants with psoriasis and NAFLD had a higher prevalence of subclinical atherosclerosis in a novel manner. In addition, those with elevated hepatic inflammation had more CVD risk factors and coronary atherosclerosis burden. Increased awareness of liver disease among patients with psoriasis and their providers is warranted.

METHODS AND MATERIALS

A total of 314 participants were included in a two-cohort, cross sectional study: European cohort (n=76 psoriasis patients, n=76 controls) and United States cohort (n=162 psoriasis patients) **(Figure 1)**. Protocols were approved by the ethics committee of Complejo Hospitalario de Toledo for the European cohort and the institutional review board of the National Institutes of Health for the United States cohort.

European cohort

Study population

Of the 234 consecutive participants recruited from May through September 2017, 51 patients with psoriasis and 31controls were excluded after application of exclusion criteria. Therefore, the final sample comprised of 76 participants with moderate to severe chronic plaque psoriasis (PASI and BSA > 10) and 76 controls matched 1:1 for sex, age and BMI. Participants were consecutively recruited at the Department of Dermatology, Hospital del Valle, Toledo, Spain. Those with a clinical diagnosis of psoriasis and no systemic psoriasis treatment in the last three months before study initiation were included. Exclusion criteria were: history of daily alcohol intake > 30 g (men) and 20 g (women), based on a validated questionnaire on alcohol consumption and confirmation of the results by a family member; the presence of hepatitis B or hepatitis C virus serological markers, autoimmune hepatitis, primary biliary cirrhosis, cancer, diabetes, or endocrine, cardiac, renal or pulmonary disease; use of drugs that might cause steatosis (such as corticosteroids, amiodarone, methotrexate, tamoxifen), chronic inflammatory disease, arthritis, or a history of cardiovascular or cerebrovascular disease. The control group consisted of individuals >18 years in age with non- inflammatory dermatological diseases other

than psoriasis (nevi, seborrheic keratosis, actinic keratosis, or verruca) and hospital paramedical and administrative personnel. Exclusion criteria for the controls were the same as described above for psoriasis participants plus the presence or family history of psoriasis.

Clinical evaluation and biochemical measurements

Low physical activity was defined as physical exercise < 30 min/day. Psoriasis severity was quantified according to PASI score and affected BSA. Arterial hypertension was defined by a systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or self-reported use of antihypertensive medication. Laboratory analysis was performed after overnight fasting. Dyslipidemia was defined by total cholesterol ≥240 mg/dL, low density lipoprotein cholesterol ≥160 mg/dL, high density lipoprotein cholesterol <40 mg/dL, or use of lipid-lowering drugs. Other data of baseline comorbidities were acquired by participant reported history of a diagnosis given by a healthcare provider.

Vascular ultrasound analysis

Participants underwent B-Mode and Doppler ultrasound examination with a MyLab 25 Gold ultrasound system (Esaote, Florence, Italy). Ultrasound images were acquired with a linear high-frequency 2-dimensional probe (6-18 MHz; Esaote LA435). Vascular ultrasound examination of the bilateral carotid and common femoral arteries was performed with methods previously described in detail.(Gonzalez-Cantero et al., 2019) Plaque was defined as a focal structure encroaching at least 0.5 mm into the arterial lumen or having a thickness ≥ 50% of the surrounding intima-media thickness. Three measurements were made of each plaque thickness and the average calculated. Subclinical atherosclerosis was defined by the presence of plaque in the carotid or femoral arteries.

Sonography for liver fat quantification

Abdominal ultrasound studies were performed with a curved phased-array abdominal transducer (1.5-10 MHz), as previously reported in detail.(Martín-Rodríguez et al., 2014) Ultrasound images of the liver and right kidney were obtained in the same sagittal view in the lateral position. SHRI was calculated as the ratio of the echogenicity of the liver to the echogenicity of the right kidney parenchyma. The optimal SHRI cutoff point for the diagnosis of NAFLD (liver fat > 5%) was 1.28, with a sensitivity of 94.67% and specificity of 95.65%. The validity of all SHRI cutoff points was previously established with 3T proton magnetic resonance spectroscopy as the gold standard.(Martín-Rodríguez et al., 2014)

United States cohort

Study population

The study consisted of 336 consecutive participants with psoriasis 18 years or older recruited from January 1, 2013 through August 11, 2020, of whom 216 had whole body PET and CCTA results. 25 participants were excluded due to excess alcohol intake (men >14 drinks/week, women >7 drinks/week with one drink approximated at about 14 grams) and 29 participants were excluded for use of systemic therapy (steroids and methotrexate). A final cohort of 162 participants were included. Psoriasis was diagnosed by a certified dermatologist or rheumatologist based on typical skin findings as well as systemic disease of the joints, nails, and hair. Psoriatic arthritis was diagnosed based on the Classification Criteria for Psoriatic Arthritis (CASPAR) by a certified rheumatologist. Additional exclusion criteria were an estimated glomerular filtration rate <30 mL/min/1.73 m^2, known current cardiovascular disease, history of hepatitis B/C or history of chronic liver disease, and conditions that increase systemic

inflammation such as internal solid or liquid malignancy within the past 5 years, human immunodeficiency virus infection, any active infection 72 hours prior, major surgery within the previous 3 months, current pregnancy, or lactation.

Clinical evaluation and biochemical measurements

Participants underwent measurement of routine vitals and gave histories of previous diagnoses and health related activities. Data of baseline comorbidities such as hypertension and diabetes were acquired by participant reported history of a diagnosis given by a healthcare provider. Psoriasis skin burden was evaluated with PASI score and affected BSA. Measurements of a fasting lipid panel, liver enzymes and inflammatory markers were performed. Metabolic syndrome was defined as meeting 3 or more of the harmonized International Diabetes Federation criteria.

Characterization of hepatic inflammation

FDG-PET imaging (Gemini TF; Philips Medical Systems, Bothell, Washington) was performed after an 8 hour fast according to methods previously described.(Mehta et al., 2011) Axial, sagittal, and coronal PET reconstructions were interpreted with and without attenuation correction using non-contrast CT images for attenuation correction and anatomical correlation of FDG uptake. After qualitative review of PET and CT images, a 3-dimensional spherical region of interest with a volume of 90 cm^3 was manually placed within the hepatic margin. Maximum SUVs were measured for the spherical volume using dedicated PET/CT image analysis software that auto-calculates the SUV per slice within the specified region of interest (Extended Brilliance Workstation; Philips Healthcare, Bothell, Washington). High maximum ^{18}F-FDG uptake was defined as $\geq$ the median uptake in the cohort (5.3 SUV).

Coronary atherosclerosis burden characterization

All participants underwent CCTA in the same scanner (320-detector row Aquilion ONE ViSION). Scans were performed with retrospective gating at 120 kV, tube current of 750-850 mA and a gantry rotation time of ≤420 milliseconds. Total, noncalcified and dense calcified burden were phenotyped for the right, left anterior descending and left circumflex coronary arteries with QAngio CT (Medis, The Netherlands) using previously described methods and adjusted for mean lumen intensity.(Salahuddin et al., 2015) Noncalcified burden subcomponents were based on Hounsfield units derived by the software. Maximum lipid rich necrotic core area was quantified with commercially available plaque quantification software (vascuCAP, Elucid Bioimaging Inc, Boston, MA) as previously described.(Choi et al., 2020) Maximum lipid rich necrotic core area did not require adjustment for lumen intensity. Guidelines established by the NIH Radiation Exposure Committee were followed.

Statistical analysis

Values are reported as mean (standard deviation) for parametric, median (interquartile range) for non-parametric, and n (%) for categorical variables. Statistical significance was assessed by Student's t-test for parametric, Wilcoxon rank-sum test for nonparametric, and Pearson's $\chi 2$ test for categorical variables. Multiple comparisons were performed with one-way analysis of variance, followed by Tukey's multiple-comparison test. Atherosclerosis burden is presented as an average of the right, left anterior descending and left circumflex coronary arteries. Logistic and linear regressions were conducted for predictors of subclinical atherosclerosis with the following covariates: age, sex, current smoking, waist circumference, HOMA-IR, systolic blood pressure, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides,

and c-reactive protein. Standardized betas were reported. P-value <.05 was considered significant.

DATA AVAILABILITY STATEMENT

Written data requests can be made to the corresponding author Nehal N. Mehta, MD after publication of the manuscript.

ORCIDS

Alvaro Gonzalez-Cantero: https://orcid.org/0000-0001-8060-4784

Meron Teklu: https://orcid.org/0000-0001-9279-3754

Alexander V Sorokin: https://orcid.org/0000-0002-2291-4888

Ronald Prussick: https://orcid.org/0000-0002-9375-2097

Jorge González-Cantero: https://orcid.org/0000-0001-9526-3919

Nidhi Patel: https://orcid.org/0000-0002-4446-0901

Philip M Parel: https://orcid.org/0000-0002-1272-3316

Grigory A Manyak: https://orcid.org/0000-0002-2409-8044

Heather L Teague: http://orcid.org/0000-0001-6013-4252

Justin A Rodante: http://orcid.org/0000-0002-2435-7747

Andrew Keel: https://orcid.org/0000-0002-8237-0480

Cristina Pérez-Hortet: https://orcid.org/0000-0002-2292-1383

Ana I Sanchéz-Moya: https://orcid.org/0000-0002-1566-9597

Natalia Jiménez: https://orcid.org/0000-0002-7206-499X

Asunción Ballester: https://orcid.org/0000-0002-6780-0390

Jorge Solis: https://orcid.org/0000-0002-4227-7062

Leticia Fernandez-Friera: https://orcid.org/0000-0002-4237-2166

María G Barderas: https://orcid.org/0000-0003-4290-4721

Jorge L Gonzalez-Calvin: https://orcid.org/0000-0002-8274-2723

Pedro Jaen: https://orcid.org/0000-0002-7334-0044

Martin P Playford: https://orcid.org/0000-0002-5571-7266

Amit K Dey: http://orcid.org/0000-0001-9916-8898

Joel M Gelfand: http://orcid.org/0000-0003-3480-2661

Nehal N Mehta: http://orcid.org/0000-0003-4939-5130

CONFLICTS OF INTEREST

Dr. Mehta is a full-time U.S. government employee and has received research grants from Abbvie, Janssen, Novartis Corp, and Celgene, outside the submitted work. Dr. Gelfand reports personal fees from Abcentra, BMS, Boehringer Ingelheim, Cara (DSMB), GSK, Lilly (DMC), Janssen Biologics, Novartis Corp, UCB (DSMB), Neuroderm (DSMB), Dr. Reddy's Labs, Happify, Inc., Mindera Dx, Pfizer Inc., and Sun Pharma and grants from Abbvie, Boehringer Ingelheim, Janssen, Novartis Corp , Celgene, Ortho Dermatologics, and Pfizer Inc, outside the submitted work. Dr. González-Cantero has served as a consultant for Abbie, Janssen, Novartis, Almirall, Celgene and Leo Pharma receiving grants/other payments, outside the submitted work. Dr Prussick has served as a consultant and/or speaker for AbbVie, Janssen, Pfizer, Novartis and Amgen/Celgene, outside the submitted work. All other authors report no conflicts of interest.

ACKNOWLEDGMENTS

This work was funded by National Heart, Lung and Blood Institute Intramural Research Program (HL006193-07). The funder was not involved in the study design, data collection, data analysis, manuscript preparation and/or publication decisions.

AUTHOR CONTRIBUTIONS STATEMENT

Conceptualization: AGC**,** MT, JGC, MPP, AKD, JMG**; Data Curation:** AGC, MT, AVS, NP, PP, MPP, AKD, NNM **; Formal Analysis:** AGC, MT **; Funding Acquisition:** AGC, NNM **; Investigation:** AGC, MT, AVS, AKD, NNM**; Methodology:** AGC, MT, AVS, RP, JGC, NP, PP, GAM, HLT, CPH, AISM, NJ, AB, JS, LFF, MGB, JLGC, PJ, MPP, AKD, NNM**; Project Administration:** AGC, MT, AVS, MPP, AKD, NNM**; Resources:** AGC, AVS, RP, JAR, AK, MPP, AKD, JMG, NNM **; Software:** AGC, MT, NNM**; Supervision:** AGC, JMG, NNM, **; Validation:** AGC, MT, NNM **; Visualization:** AGC, MT, AVS, NNM**; Writing - Original Draft Preparation:** AGC, MT, AVS, NP, NNM**; Writing - Review and Editing:** AGC, MT, AVS, RP, JGC, NP, PP, GAM, HLT, JAR, AK, CPH, AISM, NJ, AB, JS, LFF, MGB, JLGC, PJ, MPP, AKD, JMG, NNM

REFERENCES

Aksentijevich M, Lateef SS, Anzenberg P, Dey AK, Mehta NN. Chronic inflammation, cardiometabolic diseases and effects of treatment: Psoriasis as a human model. Trends Cardiovasc Med 2019.

Armstrong MJ, Gaunt P, Aithal GP, Barton D, Hull D, Parker R, et al. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. Lancet 2016;387(10019):679-90.

Campanati A, Ganzetti G, Di Sario A, Damiani A, Sandroni L, Rosa L, et al. The effect of etanercept on hepatic fibrosis risk in patients with non-alcoholic fatty liver disease, metabolic syndrome, and psoriasis. J Gastroenterol 2013;48(7):839-46.

Chatterjee PK. Hepatic inflammation and insulin resistance in pre-diabetes - further evidence for the beneficial actions of PPAR-gamma agonists and a role for SOCS-3 modulation. Br J Pharmacol 2010;160(8):1889-91.

Chen Z, Yu R, Xiong Y, Du F, Zhu S. A vicious circle between insulin resistance and inflammation in nonalcoholic fatty liver disease. Lipids Health Dis 2017;16(1):203.

Choi H, Uceda DE, Dey AK, Abdelrahman KM, Aksentijevich M, Rodante JA, et al. Treatment of Psoriasis With Biologic Therapy Is Associated With Improvement of Coronary Artery Plaque Lipid-Rich Necrotic Core: Results From a Prospective, Observational Study. Circ Cardiovasc Imaging 2020;13(9):e011199.

Crowson CS, Matteson EL, Roger VL, Therneau TM, Gabriel SE. Usefulness of risk scores to estimate the risk of cardiovascular disease in patients with rheumatoid arthritis. Am J Cardiol 2012;110(3):420-4.

Eder L, Chandran V, Gladman DD. The Framingham Risk Score underestimates the extent of subclinical atherosclerosis in patients with psoriatic disease. Ann Rheum Dis 2014;73(11):1990-6.

Gao B, Tsukamoto H. Inflammation in Alcoholic and Nonalcoholic Fatty Liver Disease: Friend or Foe? Gastroenterology 2016;150(8):1704-9.

Gehrke N, Schattenberg JM. Metabolic Inflammation-A Role for Hepatic Inflammatory Pathways as Drivers of Comorbidities in Nonalcoholic Fatty Liver Disease? Gastroenterology 2020;158(7):1929-47.e6.

Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB. Risk of myocardial infarction in patients with psoriasis. Jama 2006;296(14):1735-41.

Glaudemans AW, de Vries EF, Galli F, Dierckx RA, Slart RH, Signore A. The use of (18)F-FDG-PET/CT for diagnosis and treatment monitoring of inflammatory and infectious diseases. Clin Dev Immunol 2013;2013:623036.

Gonzalez-Cantero A, Gonzalez-Cantero J, Sanchez-Moya AI, Perez-Hortet C, Arias-Santiago S, Schoendorff-Ortega C, et al. Subclinical atherosclerosis in psoriasis. Usefulness of femoral artery ultrasound for the diagnosis, and analysis of its relationship with insulin resistance. PLoS One 2019;14(2):e0211808.

Kasper P, Martin A, Lang S, Kütting F, Goeser T, Demir M, et al. NAFLD and cardiovascular diseases: a clinical review. Clin Res Cardiol 2020.

Katsagoni CN, Georgoulis M, Papatheodoridis GV, Panagiotakos DB, Kontogianni MD. Effects of lifestyle interventions on clinical characteristics of patients with non-alcoholic fatty liver disease: A meta-analysis. Metabolism 2017;68:119-32.

Keramida G, Potts J, Bush J, Verma S, Dizdarevic S, Peters AM. Accumulation of (18)F-FDG in the liver in hepatic steatosis. AJR Am J Roentgenol 2014;203(3):643-8.

Kolossváry M, Szilveszter B, Merkely B, Maurovich-Horvat P. Plaque imaging with CT-a comprehensive review on coronary CT angiography based risk assessment. Cardiovasc Diagn Ther 2017;7(5):489-506.

Koyama Y, Brenner DA. Liver inflammation and fibrosis. J Clin Invest 2017;127(1):55-64.

Love TJ, Qureshi AA, Karlson EW, Gelfand JM, Choi HK. Prevalence of the Metabolic Syndrome in Psoriasis: Results From the National Health and Nutrition Examination Survey, 2003-2006. Archives of Dermatology 2011;147(4):419-24.

Mahfood Haddad T, Hamdeh S, Kanmanthareddy A, Alla VM. Nonalcoholic fatty liver disease and the risk of clinical cardiovascular events: A systematic review and meta-analysis. Diabetes Metab Syndr 2017;11 Suppl 1:S209-s16.

Mancini M, Prinster A, Annuzzi G, Liuzzi R, Giacco R, Medagli C, et al. Sonographic hepatic-renal ratio as indicator of hepatic steatosis: comparison with (1)H magnetic resonance spectroscopy. Metabolism 2009;58(12):1724-30.

Martín-Rodríguez JL, Arrebola JP, Jiménez-Moleón JJ, Olea N, González-Calvin JL. Sonographic quantification of a hepato-renal index for the assessment of hepatic steatosis in comparison with 3T proton magnetic resonance spectroscopy. Eur J Gastroenterol Hepatol 2014;26(1):88-94.

Mehta NN, Yu Y, Saboury B, Foroughi N, Krishnamoorthy P, Raper A, et al. 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(9):1031-9.

Meshkani R, Adeli K. Hepatic insulin resistance, metabolic syndrome and cardiovascular disease. Clin Biochem 2009;42(13-14):1331-46.

Noguchi T, Nakao K, Asaumi Y, Morita Y, Otsuka F, Kataoka Y, et al. Noninvasive Coronary Plaque Imaging. J Atheroscler Thromb 2018;25(4):281-93.

Ogdie A, Grewal SK, Noe MH, Shin DB, Takeshita J, Chiesa Fuxench ZC, et al. Risk of Incident Liver Disease in Patients with Psoriasis, Psoriatic Arthritis, and Rheumatoid Arthritis: A Population-Based Study. J Invest Dermatol 2018;138(4):760-7.

Popa C, Netea MG, van Riel PL, van der Meer JW, Stalenhoef AF. The role of TNF-alpha in chronic inflammatory conditions, intermediary metabolism, and cardiovascular risk. J Lipid Res 2007;48(4):751-62.

Prussick RB, Miele L. Nonalcoholic fatty liver disease in patients with psoriasis: a consequence of systemic inflammatory burden? Br J Dermatol 2018;179(1):16-29.

Salahuddin T, Natarajan B, Playford MP, Joshi AA, Teague H, Masmoudi Y, et al. Cholesterol efflux capacity in humans with psoriasis is inversely related to non-calcified burden of coronary atherosclerosis. Eur Heart J 2015;36(39):2662-5.

Senn JJ, Klover PJ, Nowak IA, Mooney RA. Interleukin-6 induces cellular insulin resistance in hepatocytes. Diabetes 2002;51(12):3391-9.

Stefan N, Häring HU, Cusi K. Non-alcoholic fatty liver disease: causes, diagnosis, cardiometabolic consequences, and treatment strategies. Lancet Diabetes Endocrinol 2019;7(4):313-24.

Steinl DC, Kaufmann BA. Ultrasound imaging for risk assessment in atherosclerosis. Int J Mol Sci 2015;16(5):9749-69.

Tikkanen MJ, Fayyad R, Faergeman O, Olsson AG, Wun CC, Laskey R, et al. Effect of intensive lipid lowering with atorvastatin on cardiovascular outcomes in coronary heart disease patients with mild-to-moderate baseline elevations in alanine aminotransferase levels. Int J Cardiol 2013;168(4):3846-52.

van der Voort EA, Koehler EM, Dowlatshahi EA, Hofman A, Stricker BH, Janssen HL, et al. Psoriasis is independently associated with nonalcoholic fatty liver disease in patients 55 years old or older: Results from a population-based study. J Am Acad Dermatol 2014;70(3):517-24.

van Rosendael AR, Narula J, Lin FY, van den Hoogen IJ, Gianni U, Al Hussein Alawamlh O, et al. Association of High-Density Calcified 1K Plaque With Risk of Acute Coronary Syndrome. JAMA Cardiol 2020;5(3):282-90.

Webb M, Yeshua H, Zelber-Sagi S, Santo E, Brazowski E, Halpern Z, et al. Diagnostic value of a computerized hepatorenal index for sonographic quantification of liver steatosis. AJR Am J Roentgenol 2009;192(4):909-14.

Xia MF, Yan HM, He WY, Li XM, Li CL, Yao XZ, et al. Standardized ultrasound hepatic/renal ratio and hepatic attenuation rate to quantify liver fat content: an improvement method. Obesity (Silver Spring) 2012;20(2):444-52.

Younossi ZM. Non-alcoholic fatty liver disease - A global public health perspective. J Hepatol 2019;70(3):531-44.

Table 1. Comparison of Psoriasis Participants to Controls in the European Cohort

Parameter	Psoriasis	Controls	*P* Value
Clinical Characteristics	**N=76**	**N=76**	
Age, years	45 (12)	44 (11)	matched
Sex, m/f	53/23	55/21	matched
BMI, kg/m^2	29.7 (5.58)	28.2 (4.56)	matched
Waist circumference, cm	102 (13.8)	96.7 (13.5)	**0.048**
Low physical activity, n	9 (12)	11 (14)	0.78
Smoking, n	23 (30)	13 (17)	0.08
Hypertension, n	19 (25)	9 (12)	0.10
Dyslipidemia, n	26 (34)	13 (17)	**0.046**
Psoriasis Characteristics			
PASI score	12.8 (4.67)	-	-
Disease duration, years	18 (13)	-	-
BSA, %	15.7 (9.34)	-	-
Lab Values			
Alanine aminotransferase, U/L	27.3 (19.0)	27.3 (18.8)	1.0
Aspartate aminotransferase, U/L	23.3 (11.0)	22.8 (8.25)	0.83
C-reactive protein, mg/L	3.68 (4.11)	2.04 (1.38)	**0.01**
Glucose, mg/dL	98.3 (15.8)	94.5 (8.74)	0.14
Insulin, mcU/ml	16.94 (12.67)	11.1 (6.93)	
HOMA-IR	4.30 (3.53)	2.60 (2.00)	**0.005**
Lipid Profile			
Triglycerides, mg/dL	143 (88.2)	97.9 (41.3)	**0.002**
Total cholesterol, mg/dL	191 (31.9)	194 (36.9)	0.71
HDL cholesterol, mg/dL	50.7 (13.7)	56.9 (14.1)	**0.03**
LDL cholesterol, mg/dL	112 (28.1)	116 (33.5)	0.54
Fatty Liver Parameters			
NAFLD, n	46 (61)	34 (45)	**0.04**
SHRI	1.54 (0.46)	1.34 (0.39)	**0.02**
Atherosclerosis Characteristics			
Subclinical atherosclerosis, n	35 (46)	14 (18)	**<0.001**
Femoral atheroma plaques, n	32 (42)	11 (14)	**0.001**
Carotid atheroma plaques, n	15 (20)	9 (12)	0.21

BMI, Body mass index; PASI, Psoriasis area and severity index; BSA, body surface area; HOMA-IR, homeostatic model assessment for insulin resistance; HDL, high density lipoprotein; LDL, low density lipoprotein; NAFLD, non-alcoholic fatty liver disease; SHRI, sonographic hepatorenal index. Data are expressed as mean (standard deviation) for continuous variables and n (%) for categorical variables.

Table 2. Characteristics of Psoriasis Participants from European Cohort Stratified by NAFLD Status

Parameter	NAFLD Present	NAFLD Absent	*P* Value
Clinical Characteristics	**N=46**	**N=30**	
Age, years	47 (10)	42 (13)	0.09
Sex, m/f	33/13	20/10	0.64
BMI, kg/m^2	31.8 (5.26)	26.5 (4.50)	**<0.001**
Waist circumference, cm	107 (12.6)	93.8 (11.7)	**<0.001**
Low physical activity, n	9 (20)	0 (0)	**0.03**
Smoking, n	12 (26)	11(37)	0.30
Hypertension, n	15 (33)	4 (13)	0.78
Dyslipidemia, n	21 (46)	5 (17)	**0.04**
Psoriasis Characteristics			
PASI score	12.5 (3.31)	13.2 (6.24)	0.61
BSA, %	14.3 (6.36)	17.9 (12.4)	0.20
Disease duration, years	19 (13)	16 (10)	0.43
Lab Values			
Alanine aminotransferase, U/L	33 (21)	18 (11)	**0.002**
Aspartate aminotransferase, U/L	24 (8)	22 (14)	0.51
C-reactive protein, mg/L	3.97 (3.71)	3.18 (4.81)	0.52
Glucose, mg/dL	102 (18.6)	92.2 (7.27)	**0.01**
Insulin, mcU/ml	20.7 (14.4)	10.44 (3.86)	**<0.001**
HOMA-IR	5.40 (4.00)	2.40 (0.92)	**<0.001**
Lipid Profile			
Triglycerides, mg/dL	174 (95.4)	95.1 (46.3)	**<0.001**
Total cholesterol, mg/dL	199 (32.1)	179 (28.2)	**0.02**
HDL cholesterol, mg/dL	46.7 (11.3)	56.8 (15.0)	**0.009**
LDL cholesterol, mg/dL	119 (29.9)	103 (22.4)	**0.04**
Fatty Liver Parameters			
NAFLD, n	46	-	-
SHRI	1.84 (0.36)	1.10 (0.08)	**<0.001**
Atherosclerosis Characteristics			
Subclinical atherosclerosis, n	28 (61)	7 (23)	**0.006**
Femoral atheroma plaques, n	26 (57)	6 (20)	**0.008**
Carotid atheroma plaques, n	10 (22)	5 (17)	0.59

BMI; Body mass index. PASI; Psoriasis area and severity index. BSA; body surface area. HOMA-IR; homeostatic model assessment for insulin resistance. HDL; high density lipoprotein. LDL; low density lipoprotein. NAFLD; non-alcoholic fatty liver disease. SHRI; sonographic hepatorenal index. Data are expressed as mean (standard deviation) for continuous variables and n (%) for categorical variables.

Table 3. Comparison of Psoriasis Participants and Controls Stratified by NAFLD in the European Cohort

Parameter	Psoriasis with NAFLD	Psoriasis without NAFLD	Controls with NAFLD	Controls without NAFLD
Clinical Characteristics	**N=46**	**N=30**	**N=34**	**N=42**
Age, years	47.0 (9.96)	41.9 (13.1)	46.5 (10.5)	42.5 (11.9)
Sex, m/f	33/13	20/10	26/8	29/13
BMI, kg/m^2	31.8 (5.26) [a, c]	26.5 (4.50) [b, d]	30.3 (4.31) [a, c]	26.6 (4.19) [b, d]
Waist circumference, cm	107 (12.6) [a, c]	93.8 (11.7) [b, d]	102 (12.7) [a, c]	92.9 (12.7) [b, d]
Low physical activity, n	9 (20) [a]	0 (0) [b, d]	7 (21) [a]	4 (10)
Smoking, n	12 (26)	11(37)	5 (15)	8 (19)
Hypertension, n	15 (33) [c]	4 (13)	8 (24) [c]	1(2) [b, d]
Dyslipidemia, n	21 (46) [a, c]	5 (17) [d]	9 (26)	4 (10) [d]
Psoriasis Characteristics				
PASI score	12.5 (3.31)	13.2 (6.24)	-	-
Disease duration, years	18.7 (12.7)	16.3 (9.69)	-	-
BSA, %	14.3 (6.36)	17.9 (12.4)	-	-
Lab Values				
Alanine aminotransferase, U/L	33.1 (21.0) [a, c]	18.2 (10.6) [b, d]	33.8 (20.3) [a, c]	22.7 (16.9) [b, d]
Aspartate aminotransferase, U/L	24.1 (8.31)	22.0 (14.3)	24.5 (8.35)	21.8 (8.27)
C-reactive protein, mg/L	3.97 (3.71) [b, c]	3.18 (4.81) [b, c]	1.79 (1.05) [a, d]	2.23 (1.60) [a, d]
Glucose, mg/dL	102 (18.6) [a, c]	92.2 (7.27) [d]	96.8 (10.4)	92.9 (7.22) [d]
Insulin, mcU/ml	20.7 (14.4) [a. b, c]	10.44 (3.86) [d]	12.69 (8.89) [d]	9.98 (5.09) [d]
HOMA-IR	5.40 (4.00) [a, b, c]	2.40 (0.92) [d, c]	3.18 (2.69) [c, d]	1.87 (0.57) [a, d]
Lipid Profile				
Triglycerides, mg/dL	174 (95.4) [a, b, c]	95.1 (46.3) [d]	104 (44.6) [d]	92.5 (39.2) [d]
Total cholesterol, mg/dL	199 (32.1) [a]	179 (28.2) [d]	195 (38.3)	192 (36.9)
HDL cholesterol, mg/dL	46.7 (11.3) [a, c]	56.8 (15.0) [d]	52.8 (12.2)	60.1 (15.0) [d]
LDL cholesterol, mg/dL	119 (29.9) [a]	103 (22.4) [d]	116 (31.1)	115 (36.0)
Fatty Liver Parameters				
NAFLD, n	46	-	34	-
SHRI	1.84 (0.36) [a, b, c]	1.10 (0.08) [b, d]	1.66 (0.39) [a, c, d]	1.09 (0.09) [b, d]
Atherosclerosis Characteristics				
Subclinical atherosclerosis, n	28 (61) [a, b, c]	7 (23) [d, c]	11 (32) [c, d]	3 (7) [a, b, d]
Femoral atheroma plaques, n	26 (57) [a, b, c]	6 (20) [d]	8 (24) [d]	3 (7) [d]
Carotid atheroma plaques, n	10 (22) [c]	5 (17)	8 (24) [c]	1 (2) [b, d]

[a] $p<0.05$ vs. psoriasis without NAFLD; [b] $p<0.05$ vs. controls with NAFLD; [c] $p<0.05$ vs. controls without NAFLD; [d] $p<0.05$ vs. psoriasis with NAFLD.BMI, Body mass index; PASI, Psoriasis area and severity index; BSA, body surface area; HOMA-IR, homeostatic model assessment for insulin resistance; HDL, high density lipoprotein; LDL, low density lipoprotein; NAFLD, non-alcoholic fatty liver disease; SHRI, sonographic hepatorenal index. Data are expressed as mean (standard deviation) for continuous variables and n (%) for categorical variables.

Table 4. Characteristics of the United States Cohort Stratified by Maximum Hepatic ^{18}F-FDG Uptake

Parameter	Low Uptake N=81	High Uptake N=81	*P* Value
Clinical Characteristics			
Age, years	50 (14)	51 (12)	0.44
Sex, m/f	41/40	62/19	**<0.001**
BMI, kg/m^2	27.0 (4.36)	32.9 (6.36)	**<0.001**
Waist circumference, cm	93 (84-102)	106 (94-119)	**<0.001**
Current smoker, n	11 (14)	6 (7)	0.20
Hypertension, n	15 (19)	28 (35)	**0.02**
Hyperlipidemia, n	27 (33)	38 (47)	0.08
Diabetes, n	6 (7)	6 (7)	1.00
Lipid lowering medication, n	17 (21)	34 (42)	**0.004**
Metabolic syndrome, n	16 (20)	35 (45)	**<0.001**
Psoriasis Characteristics			
PASI score	5.6 (2.7-11)	6.7 (3.6-11)	0.18
BSA, %	4.6 (2.0-17)	6.8 (3.0-16)	0.26
Disease duration, years	18 (14)	22 (12)	0.07
Psoriatic arthritis, n	14 (17)	28 (35)	**0.01**
Clinical and Lab Values			
Alanine aminotransferase, U/L	24 (17-32)	27 (20-34)	0.07
Aspartate aminotransferase, U/L	20 (17-24)	21 (18-25)	0.12
hsC-reactive protein, mg/L	1.8 (0.71-3.1)	2.3 (0.80-4.3)	0.13
Glucose, mg/dL	94 (89-101)	99 (92-107)	**0.01**
Insulin, mcU/ml	9.5 (6.6-14)	14 (9.5-22)	**<0.001**
HOMA-IR	2.2 (1.5-3.3)	3.7 (2.3-5.3)	**<0.001**
Lipid Profile			
Triglycerides, mg/dL	92 (71-127)	110 (81-174)	**0.04**
Total cholesterol, mg/dL	171 (153-203)	176 (159-196)	0.99
HDL cholesterol, mg/dL	52 (46-70)	50 (40-59)	**0.01**
LDL cholesterol, mg/dL	95 (80-116)	106 (83-116)	0.34
Coronary Atherosclerosis Characteristics			
Total burden, mm^2 (x100)	1.1 (0.42)	1.4 (0.51)	**<0.001**
Non-calcified burden, mm^2 (x100)	1.0 (0.40)	1.3 (0.49)	**<0.001**
Fibrofatty burden, mm^2 (x100)	0.11 (0.087)	0.23 (0.15)	**<0.001**
Fibrous burden, mm^2 (x100)	0.90 (0.34)	1.0 (0.37)	**0.02**
Dense-calcified burden, mm^2 (x100)	0.07 (0.08)	0.04 (0.07)	**0.03**
Lipid rich necrotic core, mm^2	3.0 (1.7)	4.3 (2.3)	**<0.001**

High uptake defined as > the median uptake in the cohort (5.3 SUV). BMI; Body mass index. BSA; body surface area. AST; Aspartate aminotransferase. ALT; Alanine aminotransferase. HDL; High density lipoprotein. LDL; Low density lipoprotein. HOMA-IR; Homeostatic model assessment for insulin resistance. PASI; Psoriasis area severity index. Data are expressed as mean (standard deviation) or median (interquartile range) for continuous variables and n (%) for categorical variables.

Table 5. Association between Hepatic Steatosis, Hepatic Inflammation and Subclinical Atherosclerosis

5a) European cohort: Hepatic steatosis and subclinical atherosclerosis in participants with psoriasis and controls

	Psoriasis			Controls		
Exposures	OR	95% CI	*P* Value	OR	95% CI	*P* Value
SHRI	5.0	1.2-20	**0.02**	2.2	1.1-16	**0.02**
SHRI model 1	3.5	1.5-24	**0.01**	1.0	0.7-13	0.06

5b) United States cohort: Hepatic inflammation and subclinical atherosclerosis in psoriasis

	Noncalcified Burden		Fibrofatty Burden		Fibrous Burden		Lipid Rich Necrotic Core	
Exposures	Stand. β	*P* Value	Stand. β	*P* Value	Stand. β	*P* Value	Stand. β	*P* Value
Liver SUV_{max}	0.48	**<0.001**	0.62	**<0.001**	0.24	**0.003**	0.29	**<0.001**
Liver SUV_{max} model 1	0.28	**<0.001**	0.49	**<0.001**	0.02	0.84	0.28	**0.003**

Model 1 adjusted for age, sex, waist circumference, the homeostatic assessment for insulin resistance, systolic blood pressure, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, lipid-lowering therapy, c-reactive protein and current smoking. SHRI: Sonographic hepatorenal index. SUV: Standard uptake value.

Figure legends

Figure 1: Figure 1. Recruitment scheme of the European and United States cohorts.

Figure 1. Recruitment Scheme

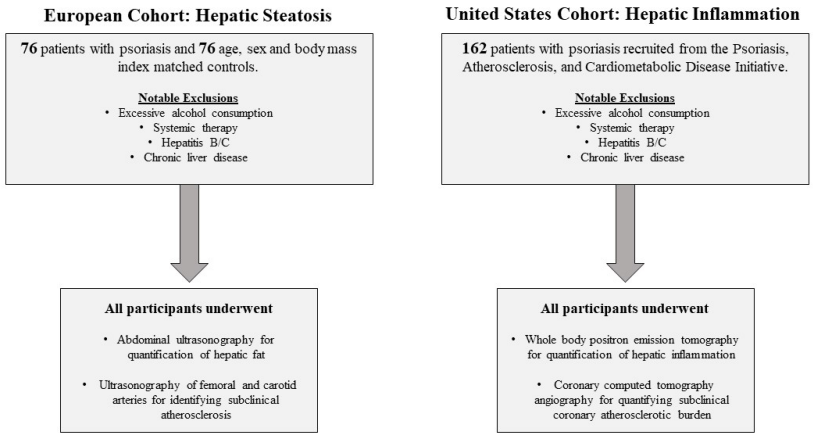

Figure 1. Recruitment scheme of the European and United States cohorts.

338x190mm (96 x 96 DPI)

Re: MS# JID-2021-0160 “Subclinical Liver Disease is Associated with Subclinical Atherosclerosis in Psoriasis: Results from Two Observational Studies”

Dear Dr. Udey, distinguished JID editorial board and reviewers,

Thank you for reviewing our manuscript titled “Subclinical Liver Disease is Associated with Subclinical Atherosclerosis in Psoriasis: Results from Two Observational Studies”. We very much appreciate the reviewers’ comments. Below, we provide point-by-point responses to reviewer comments. Thank you again for your time and consideration and we look forward to hearing from you soon.

Sincerely,

Nehal N. Mehta, MD

Reviewers' comments

Reviewer #1

Full comment: This is an interesting report, investigating liver and CVD burden in two independent cross sectional studies. The authors may wish to take into consideration the following comments before being considered for publication:

Response: Thank you for the thoughtful consideration of our work. Below we provide point-by-point responses to comments.

Full comment: Methods:
Please include the number of patients that were excluded from (each) study based on the presence of pre-existing cardiovascular disease. Hypertension, obesity, metabolic syndrome are all very common in people with psoriasis so understanding the proportion of people excluded is important.

Response: In our study, patients with known cardiovascular disease (such as myocardial infarctions, strokes, peripheral vascular disease) are not enrolled in the protocol because one of our main outcomes is the presence of *subclinical* atherosclerosis. We do not exclude participants who have risk factors for cardiovascular disease such as hypertension, obesity or the metabolic syndrome. As the reviewer notes, these are prevalent in psoriasis and we ensure that patients with these conditions are included in our protocol. We have edited our recruitment section so that it clearly states participants who were excluded after enrollment. Below are the new statements added to the manuscript for each cohort:

European cohort: "Out of the total 234 consecutive participants recruited from May through September 2017, 51 patients with psoriasis and 31control subjects were excluded after application of the exclusion criteria. Therefore, the final sample comprised of 76 participants with moderate to severe chronic plaque psoriasis (PASI and BSA > 10) and 76 healthy control subjects matched 1:1 for sex, age and BMI."

United States cohort: "The study consisted of 336 consecutive participants with psoriasis 18 years or older recruited from January 1, 2013 through August 11, 2020, of whom 216 had whole body PET and CCTA results. 25 participants were excluded due to excess alcohol intake (men >14 drinks/week, women >7 drinks/week with one drink approximated at about 14 grams) and 29 participants were excluded for use of systemic therapy (steroids and methotrexate). A final cohort of 162 participants were included."

Full comment: Patients with diabetes were excluded from the Spanish study and yet the prevalence of obesity and insulin resistance was significant. How was diabetes excluded from this group?

Response: The exclusion of participants with diabetes was based on the history of previous diagnoses. The diagnoses was either self-reported, obtained from the medical history or confirmed by review of medications. The following line has been added to the methods section:

"data of baseline comorbidities were acquired by participant reported history of a diagnosis given by a healthcare provider."

Full comment: The diagnosis of hypertension was based either on direct measurement (by whom?) or self declared. Was there any systematic bias between control and psoriasis populations on the ascertainment of clinical data? How was it decided whether or not to measure BP? To be sure that liver disease really is an independent risk factor for CVD requires careful controlling for known CVD risk factors

Response: In both studies, all participants give extensive histories of previous diagnoses, health related activities and medication use at their baseline visit during which they also underwent lab work and imaging. In the United States, hypertension was based on patient history of a diagnosis given by a healthcare provider. All participants are asked these history questions. In the European cohort, hypertension was defined by a systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or self-reported use of antihypertensive medication. A member of the healthcare team took the measurements and measurements were done in all participants. In the analysis, we adjust for systolic blood pressure in both cohorts.

Full comment: The Spanish study excluded arthritis whereas mentioned is 'joint disease' in the US study - what proportion in the US pop had psA?

Response: The United States cohort has 42 participants (26%) who met a diagnosis of psoriatic arthritis (PsA). PsA was diagnosed based on the Classification for Psoriatic Arthritis (CASPAR) criteria by a certified rheumatologist. We have added this information to the methods section and to the United States table. Though there is a higher percentage of participants with psoriatic arthritis in the high uptake group, adjusting for the presence of psoriatic arthritis does not impact the relationship between hepatic FDG uptake and coronary atherosclerosis burden in effect size or significance. We have made note of this in the revised results.

Full comment: It would be helpful if the alcohol intake units could be harmonised for the two cohorts - ie is alcohol exposure equivalent in the two pops?

Response: These differences in classification are due to the two studies being done in two different countries with different health care systems and the screening questions being asked in different manners. The European cohort used >30 g per day for men and >20 g per day for women. The United States cohort used >14 drinks/ week for women and >7 drinks/ week in men. One standard drink has about 14 grams of alcohol, which translates to about 2 drinks per day for men and one and a half drinks for women when converting the European measures. The total alcohol intake considered excessive is similar in both cohorts. We have added the statement that in the United States cohort one drink is roughly 14 grams to allow for transformation of values as needed.

Full comment: Introduction and discussion points.
The introduction could more clearly set out the hypothesis being tested. At present it is largely describing the methodology used to investigate (liver and CVD burden) which perhaps could, at least in part, be moved to the methods.

Response: We have made the introduction more clinically oriented and hypothesis driven and removed the sections discussing outcomes related to the imaging parameters. We have also clearly stated our hypothesis in the final paragraph of the introduction. Below are the specific sections added to or removed from the manuscript.

In paragraph one, we added the following section: "Traditional cardiovascular risk factors do not adequately capture risk in states of chronic inflammation, which makes the study of risk accelerators like hepatic dysfunction and their impact on directly measured atherosclerosis burden of particular importance in psoriasis.[1, 2] Despite the higher risk of liver disease in psoriasis, there are limited data on the relationship between hepatic steatosis and atherosclerosis in patients with psoriasis."

In paragraph two we refrained from specifically stating that SHRI achieves a diagnostic accuracy similar to biopsy and proton magnetic resonance spectroscopy, while still making these citations available.

In Paragraph three, we removed the following section and combined this paragraph with paragraph 4: "The presence of ultrasonographic carotid or femoral plaques predicts risk of future CVD events.[3-6] CCTA directly quantifies coronary burden and plaque characteristics beyond luminal stenosis.[7, 8] Coronary atherosclerosis burden is susceptible to modulation with statin and psoriasis specific biologic therapy.[9-12]"

In paragraph four, we added the following section: "We hypothesized that hepatic dysfunction assessed as liver fat content or inflammation would associate with markers of subclinical atherosclerosis beyond traditional cardiovascular risk factors."

Full comment: NAFLD is well established to be associated with cardiovascular disease in the general population. This study suggests that the same is true in the psoriasis population. What remains to be determined is the causal relationship between these three disease states; findings from this study, whilst definitely interesting, do not tell us whether the relationship is causal and this limitation, as well as future research needs (e.g cohort studies, Mendelian randomisation studies) could be more explicitly detailed.

Response: We agree with the reviewer that the study designs do not allow for assessment of causality and further work, through longitudinal and mechanistic studies, is needed to better understand the relationship of hepatic dysfunction to cardiometabolic consequences in psoriasis. We have added the following statement in the limitations addressing this point: "The main limitations of this study are its cross-sectional nature and relatively small sample size which limit ability to establish causality and directionality. While we illustrate an association between subclinical liver dysfunction and atherosclerosis, larger studies designed to establish causality are needed to better understand this relationship in psoriasis."

Full comment: For more clinically focused readers, perhaps some discussion about what these findings mean for clinical practice might be helpful.

Response: We have added a section at the end of the two main discussion paragraphs highlighting the importance of the findings for the clinical setting. Below are the additions.

Discussion paragraph 2: “Given the prevalence of liver disease in psoriasis, our study provides further evidence for increased clinical vigilance for the presence and consequences of hepatic dysfunction in patients with psoriasis.”

Discussion paragraph 3: “Taken together, these findings further highlight the higher prevalence of liver disease in psoriasis and the high risk atherosclerosis phenotypes associated with markers of liver disease in psoriasis. In the clinical setting, heightened awareness of the presence and consequences of hepatic dysfunction is warranted amongst patients and providers.”

Reviewer #2

Full comment: Well-written article assessing association between hepatic fat content and the presence of plaques in femoral and carotid arteries in participants with psoriasis.

The authors showed a higher prevalence of NAFLD in psoriasis compared to controls and elevated hepatic fat content in psoriasis participants with NAFLD than controls with NAFLD.

- In supplemental Table 1, we can observe that psoriasis patient with NAFLD has a SHRI à 1.84 (0.36), whereas it was at 1.66 (0.39) for patients without psoriasis, but with NAFLD. The study sample was respectively 46 and 34 patients.

Optimal SHRI cutoff point for NAFLD (>5%) diagnosis is 1.28.
SHRI cutoff point for a steatosis>25% is 1.75 (Eur J Gastroenterol Hepatol 2014;26(1):88-94)
May this authors comment the clinical pertinence between a SHRI at 1.84 and 1.66 taking into account the SD.

Response: We thank the reviewer for the interesting and valuable comments. To our knowledge, this is the first published study rigorously quantifying liver fat content in patients with psoriasis. We found, not only that patients with psoriasis had increased prevalence of NAFLD, but also that the degree of hepatic steatosis in psoriasis patients with NAFLD was greater than in controls with NAFLD (1.84 vs 1.66; $p<0.05$). This is particularly important as it has been reported that there is an association between the quantity of liver fat and the risk for cardiovascular disease in individuals with NAFLD. These findings show that psoriasis patients had a greater tendency to liver fat accumulation, which would be an important additional risk for the development of atherosclerosis. To highlight this point further in the manuscript, we have moved supplementary table 1 (which contains this data) to the main text, emphasized this finding further in the discussion and added the association between SHRI and subclinical atherosclerosis into previous table 4a (now table 5a).

Full comment: Could the authors compared SHRI between NAFLD patients with or without psoriasis adjusting for age, sex, waist circumference, the homeostatic assessment for insulin resistance, systolic blood pressure, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, lipid-lowering therapy, c-reactive protein and current smoking. Participants with psoriasis and NAFLD had a higher prevalence of subclinical atherosclerosis than those without NAFLD.

Response: we have compared SHRI between NAFLD patients with or without psoriasis adjusting for the proposed variables and the differences remains significant (p=0.043).

Full comment:

	Subclinical Atherosclerosis		
Exposures	OR	95% CI	*P* Value
SHRI	5.0	1.2-20	0.02
SHRI model 1	3.5	1.5-24	0.01

May the authors provide such results in NAFLD without psoriasis patients.

May the authors compare the association between atherosclerosis and NAFLD between psoriasis and non psoriasis patients.
This key point is to determine if psoriasis is an independent factor which increased the risk of SHRI value, and thus the risk of subclinical atherosclerosis.
These supplementary results may help to answer.

Response: We have performed the proposed analyses as follows. We have added the analyses showing the association between hepatic fat content and subclinical atherosclerosis in controls to table 4a (now table 5a) and added these results in our results section and discussion. We have noted that there is a trend towards a stronger association between hepatic fat content and subclinical atherosclerosis in psoriasis than controls, and added in our limitations paragraph that this requires further study in larger, longitudinal cohorts.

- Association between Hepatic Steatosis and Subclinical Atherosclerosis in controls with NAFLD.

	Subclinical Atherosclerosis		
Exposures	OR	95% CI	*P* Value
SHRI	2.1	1.1-15	0.03
SHRI model 1	1.3	0.9-12	0.07

- Association between Hepatic Steatosis and Subclinical Atherosclerosis in controls.

	Subclinical Atherosclerosis		
Exposures	OR	95% CI	*P* Value
SHRI	2.2	1.1-16	0.02
SHRI model 1	1.0	0.7-13	0.06

- Association between Subclinical Atherosclerosis and NAFLD in psoriasis patients.

	Subclinical Atherosclerosis		
Exposures	OR	95% CI	*P* Value
NAFLD	4.1	1.2-12	0.02
NAFLD model 1	2.7	1.1-11	0.04

- Association between Subclinical Atherosclerosis and NAFLD in controls.

	Subclinical Atherosclerosis		
Exposures	OR	95% CI	*P* Value
NAFLD	2.7	1.4-15	0.04
NAFLD model 1	1.3	0.7-16	0.07

Full comment: Minor remarks

- May the authors specify for the European cohort if cases and controls were matched for the exact age and bmi or +/- ??

Response: Psoriasis patients were carefully compared to age, sex and BMI matched non-inflamed controls whose traditional cardiovascular risk factors did not differ from the psoriasis cohort. As a result, no significant differences in age sex and BMI were found among groups, nevertheless groups were not matched for exact age and BMI.

References

1. Crowson CS, Matteson EL, Roger VL, Therneau TM, Gabriel SE. Usefulness of risk scores to estimate the risk of cardiovascular disease in patients with rheumatoid arthritis. *Am J Cardiol*. Aug 1 2012;110(3):420-4. doi:10.1016/j.amjcard.2012.03.044
2. Eder L, Chandran V, Gladman DD. The Framingham Risk Score underestimates the extent of subclinical atherosclerosis in patients with psoriatic disease. *Ann Rheum Dis*. Nov 2014;73(11):1990-6. doi:10.1136/annrheumdis-2013-203433
3. Laclaustra M, Casasnovas JA, Fernández-Ortiz A, et al. Femoral and Carotid Subclinical Atherosclerosis Association With Risk Factors and Coronary Calcium: The AWHS Study. *J Am Coll Cardiol*. Mar 22 2016;67(11):1263-74. doi:10.1016/j.jacc.2015.12.056
4. Postley JE, Luo Y, Wong ND, Gardin JM. Identification by ultrasound evaluation of the carotid and femoral arteries of high-risk subjects missed by three validated cardiovascular disease risk algorithms. *Am J Cardiol*. Nov 15 2015;116(10):1617-23. doi:10.1016/j.amjcard.2015.08.031
5. Lekakis JP, Papamichael CM, Cimponeriu AT, et al. Atherosclerotic changes of extracoronary arteries are associated with the extent of coronary atherosclerosis. *Am J Cardiol*. Apr 15 2000;85(8):949-52. doi:10.1016/s0002-9149(99)00907-8
6. Kocyigit D, Gurses KM, Taydas O, et al. Role of femoral artery ultrasound imaging in cardiovascular event risk prediction in a primary prevention cohort at a medium-term follow-up. *J Cardiol*. May 2020;75(5):537-543. doi:10.1016/j.jjcc.2019.09.012
7. Kolossváry M, Szilveszter B, Merkely B, Maurovich-Horvat P. Plaque imaging with CT-a comprehensive review on coronary CT angiography based risk assessment. *Cardiovasc Diagn Ther*. Oct 2017;7(5):489-506. doi:10.21037/cdt.2016.11.06
8. Noguchi T, Nakao K, Asaumi Y, et al. Noninvasive Coronary Plaque Imaging. *J Atheroscler Thromb*. Apr 1 2018;25(4):281-293. doi:10.5551/jat.RV17019
9. Kral BG, Becker LC, Vaidya D, et al. Noncalcified coronary plaque volumes in healthy people with a family history of early onset coronary artery disease. *Circ Cardiovasc Imaging*. May 2014;7(3):446-53. doi:10.1161/circimaging.113.000980
10. D'Ascenzo F, Cerrato E, Calcagno A, et al. High prevalence at computed coronary tomography of non-calcified plaques in asymptomatic HIV patients treated with HAART: a meta-analysis. *Atherosclerosis*. May 2015;240(1):197-204. doi:10.1016/j.atherosclerosis.2015.03.019
11. Li Z, Hou Z, Yin W, et al. Effects of statin therapy on progression of mild noncalcified coronary plaque assessed by serial coronary computed tomography angiography: A multicenter prospective study. *Am Heart J*. Oct 2016;180:29-38. doi:10.1016/j.ahj.2016.06.023
12. Elnabawi YA, Dey AK, Goyal A, et al. Coronary artery plaque characteristics and treatment with biologic therapy in severe psoriasis: results from a prospective observational study. *Cardiovasc Res*. Mar 15 2019;115(4):721-728. doi:10.1093/cvr/cvz009

Subclinical Liver Disease is Associated with Subclinical Atherosclerosis in Psoriasis: Results from Two Observational Studies

Brief title: Liver disease and atherosclerosis

Alvaro Gonzalez-Cantero, MD PhD[1*], Meron Teklu, BA[2*], Alexander V Sorokin, MD PhD[2], Ronald Prussick, MD FRCPC[3], Jorge González-Cantero, MD PhD[4], Jose Luis Martin-Rodriguez, MD[5], Nidhi Patel, BS[2], Philip M Parel [2], Grigory A Manyak, BA[2], Heather L Teague, PhD[2], Justin A Rodante, PA-C[2], Andrew Keel, CRNP[2], Cristina Pérez-Hortet, MD[6], Ana I Sanchéz-Moya, MD PhD[6], Natalia Jiménez, MD[1], Asunción Ballester, MD[1], Jorge Solis, MD, PhD[7], Leticia Fernandez-Friera, MD PhD[8], María G Barderas PhD[9], Jorge L Gonzalez-Calvin, MD PhD[10], Pedro Jaen, MD PhD[1], Martin P Playford, PhD[2,] Amit K Dey, MD[2], Joel M Gelfand, MD MSCE[11,12], Nehal N Mehta, MD MSCE FAHA[2**]

*** These authors contributed equally**

1. Department of Dermatology, Hospital Universitario Ramon y Cajal, Madrid, Spain
2. National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD, USA
3. Department of Dermatology, The George Washington School of Medicine and Health Sciences, Washington, DC, USA
4. Department of Radiology, Gregorio Marañon Hospital, Madrid, Spain
5. Department of Radiology, University Hospital San Cecilio, Granada, Spain
6. Department of Dermatology, Complejo Hospitalario de Toledo, Toledo, Spain.
7. Department of Cardiology, Hospital Universitario Doce de Octubre, Madrid, Spain
8. HM Hospitales-Centro Integral de Enfermedades Cardiovasculares HM CIEC, Madrid, Spain
9. Department of Vascular Physiopathology, Hospital Nacional de Parapléjicos, SESCAM, Toledo, Spain.
10. Department of Gastroenterology, University Hospital San Cecilio, Granada, Spain.
11. Department of Biostatistics, Epidemiology and Informatics, Perelman School of Medicine, Philadelphia, Pennsylvania, USA
12. Department of Dermatology, Perelman School of Medicine, Philadelphia, Pennsylvania, USA

**** Corresponding author:**
Nehal N. Mehta MD MSCE FAHA
Lasker Senior Investigator, Chief, Section of Inflammation and Cardiometabolic Diseases
National Heart, Lung and Blood Institute, National Institutes of Health
10 Center Drive, Clinical Research Center, Room 5-5140
Bethesda, MD 20892, USA
Telephone: 1-301-827-0483, Fax: 1-301-827-0915
Email: nehal.mehta@nih.gov

Locations of research: Toledo, Spain and Bethesda, Maryland, USA

Abbreviations

BMI; Body mass index
BSA; Body surface area
CCTA; Coronary computed tomography angiography
CVD; Cardiovascular disease
^{18}F-FDG; 2-[fluorine-18]fluoro-2-deoxy-D-glucose
NAFLD; Non-alcoholic fatty liver disease
NASH; Non-alcoholic steatohepatitis
PASI; Psoriasis area severity index
PET; Positron emission tomography
SHRI: Sonographic hepatorenal index
SUV; Standard uptake value

ABSTRACT

Psoriasis is associated with a higher risk of liver diseases. We investigated the impact of hepatic steatosis (European cohort) and hepatic inflammation (United States cohort) on subclinical atherosclerosis. In the European cohort (n=76 psoriasis participants and 76 controls), non-alcoholic fatty liver disease (NAFLD), assessed by the sonographic hepatorenal index (SHRI), was more prevalent in psoriasis than controls (61% vs 45%; p=.04). Psoriasis participants with NAFLD had a higher prevalence of subclinical atherosclerosis (ultrasonographic presence of plaque in femoral or carotid arteries) than psoriasis without NAFLD (61% vs 23%; p=.006) and controls with NAFLD (61% vs 32%; p<.05). SHRI was a determinant of subclinical atherosclerosis in psoriasis (OR, 3.5; p=.01). In the United States cohort, (n=162 psoriasis participants who underwent positron emission tomography and coronary CT angiography), those with high hepatic ^{18}F-FDG uptake had higher noncalcified (1.3 (0.49 mm^2) vs 1.0 (0.40 mm^2)), fibrofatty (0.23 (0.15 mm^2) vs 0.11 (0.087 mm^2)), and lipid rich necrotic core (4.3 (2.3 mm^2) vs 3.0 (1.7 mm^2)) coronary burden (all p<.001,). Hepatic ^{18}F-FDG uptake associated with noncalcified (β=0.28; p<.001), fibrofatty (β=0.49; p<.001) and lipid rich necrotic core (β=0.28; p=.003) burden. These results demonstrate the downstream cardiovascular effects of subclinical liver disease in psoriasis.

INTRODUCTION

Psoriasis is a chronic inflammatory condition associated with metabolic dysfunction, accelerated atherosclerosis and increased risk of myocardial infarction.(Aksentijevich et al., 2019, Gelfand et al., 2006) Psoriasis is associated with a higher incidence and prevalence of non-alcoholic fatty liver disease (NAFLD) than the general population and the risk of liver disease increases with body surface area affected by psoriasis.(Ogdie et al., 2018, van der Voort et al., 2014) NAFLD is a chronic low-grade inflammatory condition with well-known cardiovascular disease (CVD) risk.(Mahfood Haddad et al., 2017) NAFLD exhibits a spectrum of disease ranging from steatosis to the more aggressive necro-inflammatory non-alcoholic steatohepatitis (NASH), which can result in liver fibrosis and cirrhosis.(Stefan et al., 2019) Chronic systemic inflammation is central to psoriasis, NAFLD and atherosclerosis.(Aksentijevich et al., 2019, Prussick and Miele, 2018). Traditional cardiovascular risk factors do not adequately capture risk in states of chronic inflammation, making the study of risk accelerators like hepatic dysfunction and their impact on directly measured atherosclerosis burden of particular importance in psoriasis.(Crowson et al., 2012, Eder et al., 2014) Despite the higher risk of liver disease in psoriasis, there are limited data on the relationship between hepatic steatosis and atherosclerosis in patients with psoriasis.

The computerized sonographic hepatorenal index (SHRI) is a noninvasive, accurate, and validated tool for the diagnosis and quantification of liver fat. (Mancini et al., 2009, Webb et al., 2009, Xia et al., 2012) Similarly, positron emission tomography (PET) is an emerging valuable tool within inflammatory conditions. (Glaudemans et al., 2013, Mehta et al., 2011) Maximum hepatic 2-[fluorine-18]fluoro-2-deoxy-D-glucose (^{18}F-FDG) has been shown to represent irreversible uptake within inflammatory cells in the liver and therefore may be utilized as an

indicator of true hepatic inflammation.(Keramida et al., 2014) Hepatic inflammation is associated with systemic metabolic consequences and progression of NAFLD to steatohepatitis and fibrosis.(Chen et al., 2017, Gao and Tsukamoto, 2016, Gehrke and Schattenberg, 2020)

Ultrasound of vessels to identify plaques, and use of coronary computed tomography angiography (CCTA) to assess coronary atherosclerosis burden allow for non-invasive detection of subclinical atherosclerosis prior to the development of hard cardiovascular events.(Kolossváry et al., 2017, Noguchi et al., 2018, Steinl and Kaufmann, 2015) We hypothesized that hepatic dysfunction assessed as liver fat content or inflammation would associate with markers of subclinical atherosclerosis beyond traditional cardiovascular risk factors. We therefore conducted a two-stage study to assess the impact of liver disease on subclinical atherosclerosis in psoriasis. In part 1 (henceforth European cohort), we evaluated hepatic fat content and the presence of plaques in femoral and carotid arteries in controls and participants with psoriasis. In part 2 (henceforth United States cohort), we utilized hepatic ^{18}F-FDG uptake to assess liver inflammation and its impact on CCTA based coronary atherosclerosis burden in psoriasis.

RESULTS

European cohort

Comparison of participants with psoriasis to age, sex and BMI matched controls

The psoriasis cohort had a mean age of 45 years, was predominantly male (70%) and had an overweight body mass index (BMI) profile (29.7 (5.58 kg/m^2)). There was moderate to severe skin disease severity as measured by the psoriasis area severity index (PASI) score (12.8 (4.67)) and affected body surface area (BSA) (15.7 (9.34 %)) and an average disease duration of 18 years. When compared to healthy controls matched 1:1 for age, sex and BMI, participants with

psoriasis had higher waist circumferences (102 (13.8 cm) vs 96.7 (13.5 cm); p=.048), prevalence of dyslipidemia (34% vs 17%; p=.046), c-reactive protein (3.68 (4.11 mg/L) vs 2.04 (1.38 mg/L); p=.01), homeostatic model for assessment of insulin resistance (HOMA-IR) (4.30 (3.53) vs 2.60 (2.00); p=.005) and triglycerides (143 (88.2 mg/dL) vs 97.9 (41.3 mg/dL); p=.002). There was lower high density lipoprotein cholesterol (50.7 (13.7 mg/dL) vs 56.9 (14.1 mg/dL); p=.03) in the psoriasis cohort. Participants with psoriasis had a higher prevalence of NAFLD (61% vs 45%; p=.04) and subclinical atherosclerosis (46% vs 18%; p<.001) **(Table 1).**

Comparison of psoriasis participants with and without NAFLD

Of the 76 participants with psoriasis, 46 met criteria for NAFLD. The NAFLD absent and present groups were similar in PASI scores, BSA and disease duration. The NAFLD group had higher waist circumferences (107 (12.6 cm) vs 93.8 (11.7 cm); p<.001) and percentage of participants with low physical activity (20% vs 0%; p=.03) and dyslipidemia (46% vs 17% ; p=.04). While c-reactive protein did not differ between the two groups, the NAFLD group had higher alanine aminotransferase (33 (21 U/L) vs 18 (11 U/L); p=.002) and HOMA-IR (5.40 (4.00) vs 2.40 (0.92); p<.001). Triglycerides (174 (95.4 mg/dL) vs 95.1 (46.3 mg/dL); p<.001) and low density lipoprotein cholesterol (119 (29.9 mg/dL) vs 103 (22.4 mg/dL); p=.04) were higher and high density lipoprotein cholesterol lower (46.7 (11.3 mg/dL) vs 56.8 (15.0 mg/dL); p=.009) in the NAFLD group. The NAFLD group had a higher percentage of participants with subclinical atherosclerosis (61% vs 23%; p=.006) **(Table 2).**

Comparison of psoriasis participants and controls with NAFLD

Psoriasis participants with NAFLD had higher c-reactive protein (3.97 (3.71 mg/L) vs 1.79 (1.05 mg/L)), HOMA-IR (5.40 (4.00) vs 3.18 (2.69)) and triglycerides (174 (95.4 mg/dL) vs 104 (44.6

mg/dL)), all p<.05, when compared to controls with NAFLD. Hepatic fat content (1.84 (0.36) vs 1.66 (0.39); p<.05) and presence of subclinical atherosclerosis (61% vs 32%; p<.05) were higher in psoriasis participants with NAFLD than controls with NAFLD **(Table 3).**

United States cohort

Comparison of psoriasis participants with low and high hepatic ^{18}F-FDG uptake

The cohort had a mean age of 50 years, was predominantly male (64%) and had a high BMI profile (30.0 (6.19 kg/m^2)). There was mild to moderate skin disease severity as measured by PASI score (6.3 (3.2-11)) and BSA (5.6 (2.5-16 %)) and an average disease duration of 20 years (13). The high and low hepatic ^{18}F-FDG uptake groups were similar in PASI scores and BSA, but the high uptake group had a higher percentage of participants with psoriatic arthritis (35% vs 17%; p=.01). Disease duration was higher in the high uptake group but did not meet significance (22 (12 years) vs 18 (14 years); p=.07). The high uptake group had significantly higher proportions of men (77% vs 51%; p<.001) and participants on lipid lowering therapy (42% vs 21%; p=.004). The high uptake group had higher waist circumferences (106 (94-119 cm) vs 93 (84-102 cm); p<.001) and prevalence of metabolic syndrome (45% vs 20%; p<.001). While high sensitivity c-reactive protein did not differ between the two groups, the high uptake group had higher HOMA-IR (3.7 (2.3-5.3) vs 2.2 (1.5-3.3); p<.001), and triglycerides (110 (81-174 mg/dL) vs 92 (71-127 mg/dL); p=.04) as well as lower high density lipoprotein cholesterol (50 (40-59 mg/dL) vs 52 (46-70 mg/dL); p=.01). Those with high hepatic uptake had higher total (1.4 (0.51 mm^2) vs 1.1 (0.42 mm^2); p<.001), noncalcified (1.3 (0.49 mm^2) vs 1.0 (0.40 mm^2); p<.001), fibrofatty (0.23 (0.15 mm^2) vs 0.11 (0.087 mm^2); p<.001), fibrous (1.0 (0.37 mm^2) vs 0.90 (0.34 mm^2); p=.02), and lipid rich necrotic core (4.3 (2.3 mm^2) vs 3.0 (1.7 mm^2); p<.001) coronary

burden. Dense calcified burden was higher in those with low uptake (0.07 (0.08 mm^2) vs 0.04 (0.07 mm^2); p=.03) **(Table 4).**

Association between hepatic steatosis, hepatic inflammation and subclinical atherosclerosis

In logistic regression analysis for participants with psoriasis from the European cohort, SHRI was a significant determinant of subclinical atherosclerosis (odds ratio=5.0; 95% confidence interval: 1.2-20; p=.02). After adjusting for age, sex, current smoking, waist circumference, HOMA-IR, systolic blood pressure, high density lipoprotein cholesterol, low density lipoprotein cholesterol, triglycerides, and c-reactive protein, the relationship remained significant (odds ratio=3.5; 95% confidence interval: 1.5-24; p=.01). In controls, SHRI associated with subclinical atherosclerosis in unadjusted models (odds ratio=2.2; 95% confidence interval: 1.1-16; p=.02), but the relationship became insignificant after adjustment for the above covariates (odds ratio=1.0; 95% confidence interval: 0.7-13; p=.06) **(Table 5a)**. The maximum hepatic ^{18}F-FDG uptake significantly associated with noncalcified (β=0.48; p<.001), fibrofatty (β=0.62; p<.001), fibrous (β=0.24; p=.003) and lipid rich necrotic core (β=0.29; p<.001) coronary burden in participants with psoriasis from the United States cohort. After adjusting for the above covariates, hepatic ^{18}F-FDG uptake remained significantly associated with noncalcified (β=0.28; p<.001), fibrofatty (β=0.49; p<.001) and lipid rich necrotic core (β=0.28; p=.003) coronary burden **(Table 5b).** Adjusting for the presence of psoriatic arthritis did not affect these relationships.

DISCUSSION

In this two-stage, cross-sectional study, we showed a higher prevalence of NAFLD in psoriasis compared to controls and elevated hepatic fat content in psoriasis participants with NAFLD than

controls with NAFLD. Participants with psoriasis and NAFLD had a higher prevalence of subclinical atherosclerosis than psoriasis participants without NAFLD and controls with NAFLD. SHRI, a measure of hepatic fat content, was a significant determinant of the presence of subclinical atherosclerosis in psoriasis after adjustment for traditional cardiovascular risk factors. Interestingly, there appears to be a trend of a stronger association between hepatic fat content and subclinical atherosclerosis in psoriasis than controls. Given the importance of hepatic inflammation in NAFLD, we utilized the United States cohort to assess the association between hepatic inflammation and direct coronary atherosclerosis burden. We showed that those with high hepatic ^{18}F-FDG uptake were more metabolically deranged and had a higher burden of noncalcified, fibrofatty, fibrous and lipid rich necrotic core as assessed by CCTA. In addition, hepatic ^{18}F-FDG significantly associated with high risk coronary atherosclerosis burden in fully adjusted models. Together, these findings further demonstrate the importance of liver disease in psoriasis.

Twenty-five percent of the global population has NAFLD with continued increasing incidence.(Younossi, 2019) NAFLD and its associated metabolic derangements such as adiposity, metabolic syndrome and insulin resistance are known to be more prevalent in patients with psoriasis.(Love et al., 2011, van der Voort et al., 2014) Both NAFLD and psoriasis are associated with an increased risk of CVD, with both conditions known to accelerate atherosclerosis.(Aksentijevich et al., 2019, Kasper et al., 2020) Thus, understanding the contribution of NAFLD in psoriasis to subclinical atherosclerosis is of great importance. In this study, we showed that the presence of femoral or carotid atheromas is more prevalent in participants with psoriasis and NAFLD when compared to psoriasis without NAFLD and controls with NAFLD. Furthermore, hepatic fat content was higher in participants with psoriasis

and NAFLD when compared to controls with NAFLD and was a significant determinant of subclinical atherosclerosis independent of traditional cardiovascular risk factors in psoriasis. While the mechanistic link between NAFLD and CVD risk is complex, it is known that the consequential dyslipidemia and insulin resistance, both of which are higher in states of chronic inflammation and in our psoriasis cohort with NAFLD, play an important role.(Kasper et al., 2020) Lifestyle modifications and pharmacologic interventions have been shown to reduce the extent of NAFLD and its CVD risk.(Armstrong et al., 2016, Campanati et al., 2013, Katsagoni et al., 2017, Tikkanen et al., 2013) Given the prevalence of liver disease in psoriasis, our study provides further evidence for increased clinical vigilance for the presence and consequences of hepatic dysfunction in patients with psoriasis.

Hepatic inflammation is associated with insulin resistance, elevated lipid levels and the metabolic syndrome, all factors significantly elevated in our cohort with high hepatic ^{18}F-FDG uptake and factors important for the development and progression of NAFLD.(Chatterjee, 2010, Meshkani and Adeli, 2009, Popa et al., 2007, Senn et al., 2002) Lipid accumulation in hepatocytes can trigger localized inflammation and the resulting damage creates a feedback loop that aggravates inflammation. This phenomenon is important in the progression of NAFLD, NASH and cirrhosis and increases comorbidities associated with NAFLD.(Gehrke and Schattenberg, 2020, Koyama and Brenner, 2017) While the quantification of inflammation in the liver is complicated by the relationship between ^{18}F-FDG kinetics and hepatocyte biology, there is evidence supporting the use of the maximum standard uptake value (SUV) as a marker of true and irreversible uptake of ^{18}F-FDG in the inflammatory cells within the liver.(Keramida et al., 2014) The European cohort showed that hepatic steatosis was higher in psoriasis and associates with subclinical atherosclerosis. Results from the United States cohort buttress these findings by

showing that participants with psoriasis and high hepatic inflammation had higher levels of metabolic abnormalities and direct measures of coronary atherosclerosis burden. Of note, dense calcified burden, a more stable atherosclerosis burden subtype (van Rosendael et al., 2020), was higher in those with low hepatic uptake. Furthermore, ^{18}F-FDG significantly associated with high risk atherosclerosis features such as noncalcified and lipid rich necrotic core burden independent of traditional cardiovascular risk factors. Taken together, these findings further highlight the higher prevalence of liver disease in psoriasis and the high risk atherosclerosis phenotypes associated with markers of liver disease in psoriasis. In the clinical setting, heightened awareness of the presence and consequences of hepatic dysfunction is warranted amongst patients and providers.

The main limitations of this study are its cross-sectional nature and relatively small sample size which limit ability to establish causality and directionality. While we illustrate an association between subclinical liver dysfunction and atherosclerosis, larger studies designed to establish causality are needed to better understand this relationship in psoriasis. Larger studies are also needed to confirm the trend towards a stronger association between SHRI and subclinical atherosclerosis in psoriasis compared to controls.

In conclusion, we showed that participants with psoriasis and NAFLD had a higher prevalence of subclinical atherosclerosis in a novel manner. In addition, those with elevated hepatic inflammation had more CVD risk factors and coronary atherosclerosis burden. Increased awareness of liver disease among patients with psoriasis and their providers is warranted.

METHODS AND MATERIALS

A total of 314 participants were included in a two-cohort, cross sectional study: European cohort (n=76 psoriasis patients, n=76 controls) and United States cohort (n=162 psoriasis patients) **(Figure 1)**. Protocols were approved by the ethics committee of Complejo Hospitalario de Toledo for the European cohort and the institutional review board of the National Institutes of Health for the United States cohort.

European cohort

Study population

Of the 234 consecutive participants recruited from May through September 2017, 51 patients with psoriasis and 31controls were excluded after application of exclusion criteria. Therefore, the final sample comprised of 76 participants with moderate to severe chronic plaque psoriasis (PASI and BSA > 10) and 76 controls matched 1:1 for sex, age and BMI. Participants were consecutively recruited at the Department of Dermatology, Hospital del Valle, Toledo, Spain. Those with a clinical diagnosis of psoriasis and no systemic psoriasis treatment in the last three months before study initiation were included. Exclusion criteria were: history of daily alcohol intake > 30 g (men) and 20 g (women), based on a validated questionnaire on alcohol consumption and confirmation of the results by a family member; the presence of hepatitis B or hepatitis C virus serological markers, autoimmune hepatitis, primary biliary cirrhosis, cancer, diabetes, or endocrine, cardiac, renal or pulmonary disease; use of drugs that might cause steatosis (such as corticosteroids, amiodarone, methotrexate, tamoxifen), chronic inflammatory disease, arthritis, or a history of cardiovascular or cerebrovascular disease. The control group consisted of individuals >18 years in age with non- inflammatory dermatological diseases other

than psoriasis (nevi, seborrheic keratosis, actinic keratosis, or verruca) and hospital paramedical and administrative personnel. Exclusion criteria for the controls were the same as described above for psoriasis participants plus the presence or family history of psoriasis.

Clinical evaluation and biochemical measurements

Low physical activity was defined as physical exercise < 30 min/day. Psoriasis severity was quantified according to PASI score and affected BSA. Arterial hypertension was defined by a systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or self-reported use of antihypertensive medication. Laboratory analysis was performed after overnight fasting. Dyslipidemia was defined by total cholesterol ≥240 mg/dL, low density lipoprotein cholesterol ≥160 mg/dL, high density lipoprotein cholesterol <40 mg/dL, or use of lipid-lowering drugs. Other data of baseline comorbidities were acquired by participant reported history of a diagnosis given by a healthcare provider.

Vascular ultrasound analysis

Participants underwent B-Mode and Doppler ultrasound examination with a MyLab 25 Gold ultrasound system (Esaote, Florence, Italy). Ultrasound images were acquired with a linear high-frequency 2-dimensional probe (6-18 MHz; Esaote LA435). Vascular ultrasound examination of the bilateral carotid and common femoral arteries was performed with methods previously described in detail.(Gonzalez-Cantero et al., 2019) Plaque was defined as a focal structure encroaching at least 0.5 mm into the arterial lumen or having a thickness ≥ 50% of the surrounding intima-media thickness. Three measurements were made of each plaque thickness and the average calculated. Subclinical atherosclerosis was defined by the presence of plaque in the carotid or femoral arteries.

Sonography for liver fat quantification

Abdominal ultrasound studies were performed with a curved phased-array abdominal transducer (1.5-10 MHz), as previously reported in detail.(Martín-Rodríguez et al., 2014) Ultrasound images of the liver and right kidney were obtained in the same sagittal view in the lateral position. SHRI was calculated as the ratio of the echogenicity of the liver to the echogenicity of the right kidney parenchyma. The optimal SHRI cutoff point for the diagnosis of NAFLD (liver fat > 5%) was 1.28, with a sensitivity of 94.67% and specificity of 95.65%. The validity of all SHRI cutoff points was previously established with 3T proton magnetic resonance spectroscopy as the gold standard.(Martín-Rodríguez et al., 2014)

United States cohort

Study population

The study consisted of 336 consecutive participants with psoriasis 18 years or older recruited from January 1, 2013 through August 11, 2020, of whom 216 had whole body PET and CCTA results. 25 participants were excluded due to excess alcohol intake (men >14 drinks/week, women >7 drinks/week with one drink approximated at about 14 grams) and 29 participants were excluded for use of systemic therapy (steroids and methotrexate). A final cohort of 162 participants were included. Psoriasis was diagnosed by a certified dermatologist or rheumatologist based on typical skin findings as well as systemic disease of the joints, nails, and hair. Psoriatic arthritis was diagnosed based on the Classification Criteria for Psoriatic Arthritis (CASPAR) by a certified rheumatologist. Additional exclusion criteria were an estimated glomerular filtration rate <30 mL/min/1.73 m^2, known current cardiovascular disease, history of hepatitis B/C or history of chronic liver disease, and conditions that increase systemic

inflammation such as internal solid or liquid malignancy within the past 5 years, human immunodeficiency virus infection, any active infection 72 hours prior, major surgery within the previous 3 months, current pregnancy, or lactation.

Clinical evaluation and biochemical measurements

Participants underwent measurement of routine vitals and gave histories of previous diagnoses and health related activities. Data of baseline comorbidities such as hypertension and diabetes were acquired by participant reported history of a diagnosis given by a healthcare provider. Psoriasis skin burden was evaluated with PASI score and affected BSA. Measurements of a fasting lipid panel, liver enzymes and inflammatory markers were performed. Metabolic syndrome was defined as meeting 3 or more of the harmonized International Diabetes Federation criteria.

Characterization of hepatic inflammation

FDG-PET imaging (Gemini TF; Philips Medical Systems, Bothell, Washington) was performed after an 8 hour fast according to methods previously described.(Mehta et al., 2011) Axial, sagittal, and coronal PET reconstructions were interpreted with and without attenuation correction using non-contrast CT images for attenuation correction and anatomical correlation of FDG uptake. After qualitative review of PET and CT images, a 3-dimensional spherical region of interest with a volume of 90 cm^3 was manually placed within the hepatic margin. Maximum SUVs were measured for the spherical volume using dedicated PET/CT image analysis software that auto-calculates the SUV per slice within the specified region of interest (Extended Brilliance Workstation; Philips Healthcare, Bothell, Washington). High maximum ^{18}F-FDG uptake was defined as $\geq$ the median uptake in the cohort (5.3 SUV).

Coronary atherosclerosis burden characterization

All participants underwent CCTA in the same scanner (320-detector row Aquilion ONE ViSION). Scans were performed with retrospective gating at 120 kV, tube current of 750-850 mA and a gantry rotation time of ≤420 milliseconds. Total, noncalcified and dense calcified burden were phenotyped for the right, left anterior descending and left circumflex coronary arteries with QAngio CT (Medis, The Netherlands) using previously described methods and adjusted for mean lumen intensity.(Salahuddin et al., 2015) Noncalcified burden subcomponents were based on Hounsfield units derived by the software. Maximum lipid rich necrotic core area was quantified with commercially available plaque quantification software (vascuCAP, Elucid Bioimaging Inc, Boston, MA) as previously described.(Choi et al., 2020) Maximum lipid rich necrotic core area did not require adjustment for lumen intensity. Guidelines established by the NIH Radiation Exposure Committee were followed.

Statistical analysis

Values are reported as mean (standard deviation) for parametric, median (interquartile range) for non-parametric, and n (%) for categorical variables. Statistical significance was assessed by Student's t-test for parametric, Wilcoxon rank-sum test for nonparametric, and Pearson's $\chi 2$ test for categorical variables. Multiple comparisons were performed with one-way analysis of variance, followed by Tukey's multiple-comparison test. Atherosclerosis burden is presented as an average of the right, left anterior descending and left circumflex coronary arteries. Logistic and linear regressions were conducted for predictors of subclinical atherosclerosis with the following covariates: age, sex, current smoking, waist circumference, HOMA-IR, systolic blood pressure, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides,

and c-reactive protein. Standardized betas were reported. P-value <.05 was considered significant.

DATA AVAILABILITY STATEMENT

Written data requests can be made to the corresponding author Nehal N. Mehta, MD after publication of the manuscript.

ORCIDS

Alvaro Gonzalez-Cantero: https://orcid.org/0000-0001-8060-4784

Meron Teklu: https://orcid.org/0000-0001-9279-3754

Alexander V Sorokin: https://orcid.org/0000-0002-2291-4888

Ronald Prussick: https://orcid.org/0000-0002-9375-2097

Jorge González-Cantero: https://orcid.org/0000-0001-9526-3919

Nidhi Patel: https://orcid.org/0000-0002-4446-0901

Philip M Parel: https://orcid.org/0000-0002-1272-3316

Grigory A Manyak: https://orcid.org/0000-0002-2409-8044

Heather L Teague: http://orcid.org/0000-0001-6013-4252

Justin A Rodante: http://orcid.org/0000-0002-2435-7747

Andrew Keel: https://orcid.org/0000-0002-8237-0480

Cristina Pérez-Hortet: https://orcid.org/0000-0002-2292-1383

Ana I Sanchéz-Moya: https://orcid.org/0000-0002-1566-9597

Natalia Jiménez: https://orcid.org/0000-0002-7206-499X

Asunción Ballester: https://orcid.org/0000-0002-6780-0390

Jorge Solis: https://orcid.org/0000-0002-4227-7062

Leticia Fernandez-Friera: https://orcid.org/0000-0002-4237-2166

María G Barderas: https://orcid.org/0000-0003-4290-4721

Jorge L Gonzalez-Calvin: https://orcid.org/0000-0002-8274-2723

Pedro Jaen: https://orcid.org/0000-0002-7334-0044

Martin P Playford: https://orcid.org/0000-0002-5571-7266

Amit K Dey: http://orcid.org/0000-0001-9916-8898

Joel M Gelfand: http://orcid.org/0000-0003-3480-2661

Nehal N Mehta: http://orcid.org/0000-0003-4939-5130

CONFLICTS OF INTEREST

Dr. Mehta is a full-time U.S. government employee and has received research grants from Abbvie, Janssen, Novartis Corp, and Celgene, outside the submitted work. Dr. Gelfand reports personal fees from Abcentra, BMS, Boehringer Ingelheim, Cara (DSMB), GSK, Lilly (DMC), Janssen Biologics, Novartis Corp, UCB (DSMB), Neuroderm (DSMB), Dr. Reddy's Labs, Happify, Inc., Mindera Dx, Pfizer Inc., and Sun Pharma and grants from Abbvie, Boehringer Ingelheim, Janssen, Novartis Corp , Celgene, Ortho Dermatologics, and Pfizer Inc, outside the submitted work. Dr. González-Cantero has served as a consultant for Abbie, Janssen, Novartis, Almirall, Celgene and Leo Pharma receiving grants/other payments, outside the submitted work. Dr Prussick has served as a consultant and/or speaker for AbbVie, Janssen, Pfizer, Novartis and Amgen/Celgene, outside the submitted work. All other authors report no conflicts of interest.

ACKNOWLEDGMENTS

This work was funded by National Heart, Lung and Blood Institute Intramural Research Program (HL006193-07). The funder was not involved in the study design, data collection, data analysis, manuscript preparation and/or publication decisions.

AUTHOR CONTRIBUTIONS STATEMENT

Conceptualization: AGC**,** MT, JGC, MPP, AKD, JMG**; Data Curation:** AGC, MT, AVS, NP, PP, MPP, AKD, NNM **; Formal Analysis:** AGC, MT **; Funding Acquisition:** AGC, NNM **; Investigation:** AGC, MT, AVS, AKD, NNM**; Methodology:** AGC, MT, AVS, RP, JGC, NP, PP, GAM, HLT, CPH, AISM, NJ, AB, JS, LFF, MGB, JLGC, PJ, MPP, AKD, NNM**; Project Administration:** AGC, MT, AVS, MPP, AKD, NNM**; Resources:** AGC, AVS, RP, JAR, AK, MPP, AKD, JMG, NNM **; Software:** AGC, MT, NNM**; Supervision:** AGC, JMG, NNM, **; Validation:** AGC, MT, NNM **; Visualization:** AGC, MT, AVS, NNM**; Writing - Original Draft Preparation:** AGC, MT, AVS, NP, NNM**; Writing - Review and Editing:** AGC, MT, AVS, RP, JGC, NP, PP, GAM, HLT, JAR, AK, CPH, AISM, NJ, AB, JS, LFF, MGB, JLGC, PJ, MPP, AKD, JMG, NNM

REFERENCES

Aksentijevich M, Lateef SS, Anzenberg P, Dey AK, Mehta NN. Chronic inflammation, cardiometabolic diseases and effects of treatment: Psoriasis as a human model. Trends Cardiovasc Med 2019.

Armstrong MJ, Gaunt P, Aithal GP, Barton D, Hull D, Parker R, et al. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. Lancet 2016;387(10019):679-90.

Campanati A, Ganzetti G, Di Sario A, Damiani A, Sandroni L, Rosa L, et al. The effect of etanercept on hepatic fibrosis risk in patients with non-alcoholic fatty liver disease, metabolic syndrome, and psoriasis. J Gastroenterol 2013;48(7):839-46.

Chatterjee PK. Hepatic inflammation and insulin resistance in pre-diabetes - further evidence for the beneficial actions of PPAR-gamma agonists and a role for SOCS-3 modulation. Br J Pharmacol 2010;160(8):1889-91.

Chen Z, Yu R, Xiong Y, Du F, Zhu S. A vicious circle between insulin resistance and inflammation in nonalcoholic fatty liver disease. Lipids Health Dis 2017;16(1):203.

Choi H, Uceda DE, Dey AK, Abdelrahman KM, Aksentijevich M, Rodante JA, et al. Treatment of Psoriasis With Biologic Therapy Is Associated With Improvement of Coronary Artery Plaque Lipid-Rich Necrotic Core: Results From a Prospective, Observational Study. Circ Cardiovasc Imaging 2020;13(9):e011199.

Crowson CS, Matteson EL, Roger VL, Therneau TM, Gabriel SE. Usefulness of risk scores to estimate the risk of cardiovascular disease in patients with rheumatoid arthritis. Am J Cardiol 2012;110(3):420-4.

Eder L, Chandran V, Gladman DD. The Framingham Risk Score underestimates the extent of subclinical atherosclerosis in patients with psoriatic disease. Ann Rheum Dis 2014;73(11):1990-6.

Gao B, Tsukamoto H. Inflammation in Alcoholic and Nonalcoholic Fatty Liver Disease: Friend or Foe? Gastroenterology 2016;150(8):1704-9.

Gehrke N, Schattenberg JM. Metabolic Inflammation-A Role for Hepatic Inflammatory Pathways as Drivers of Comorbidities in Nonalcoholic Fatty Liver Disease? Gastroenterology 2020;158(7):1929-47.e6.

Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB. Risk of myocardial infarction in patients with psoriasis. Jama 2006;296(14):1735-41.

Glaudemans AW, de Vries EF, Galli F, Dierckx RA, Slart RH, Signore A. The use of (18)F-FDG-PET/CT for diagnosis and treatment monitoring of inflammatory and infectious diseases. Clin Dev Immunol 2013;2013:623036.

Gonzalez-Cantero A, Gonzalez-Cantero J, Sanchez-Moya AI, Perez-Hortet C, Arias-Santiago S, Schoendorff-Ortega C, et al. Subclinical atherosclerosis in psoriasis. Usefulness of femoral artery ultrasound for the diagnosis, and analysis of its relationship with insulin resistance. PLoS One 2019;14(2):e0211808.

Kasper P, Martin A, Lang S, Kütting F, Goeser T, Demir M, et al. NAFLD and cardiovascular diseases: a clinical review. Clin Res Cardiol 2020.

Katsagoni CN, Georgoulis M, Papatheodoridis GV, Panagiotakos DB, Kontogianni MD. Effects of lifestyle interventions on clinical characteristics of patients with non-alcoholic fatty liver disease: A meta-analysis. Metabolism 2017;68:119-32.

Keramida G, Potts J, Bush J, Verma S, Dizdarevic S, Peters AM. Accumulation of (18)F-FDG in the liver in hepatic steatosis. AJR Am J Roentgenol 2014;203(3):643-8.

Kolossváry M, Szilveszter B, Merkely B, Maurovich-Horvat P. Plaque imaging with CT-a comprehensive review on coronary CT angiography based risk assessment. Cardiovasc Diagn Ther 2017;7(5):489-506.

Koyama Y, Brenner DA. Liver inflammation and fibrosis. J Clin Invest 2017;127(1):55-64.

Love TJ, Qureshi AA, Karlson EW, Gelfand JM, Choi HK. Prevalence of the Metabolic Syndrome in Psoriasis: Results From the National Health and Nutrition Examination Survey, 2003-2006. Archives of Dermatology 2011;147(4):419-24.

Mahfood Haddad T, Hamdeh S, Kanmanthareddy A, Alla VM. Nonalcoholic fatty liver disease and the risk of clinical cardiovascular events: A systematic review and meta-analysis. Diabetes Metab Syndr 2017;11 Suppl 1:S209-s16.

Mancini M, Prinster A, Annuzzi G, Liuzzi R, Giacco R, Medagli C, et al. Sonographic hepatic-renal ratio as indicator of hepatic steatosis: comparison with (1)H magnetic resonance spectroscopy. Metabolism 2009;58(12):1724-30.

Martín-Rodríguez JL, Arrebola JP, Jiménez-Moleón JJ, Olea N, González-Calvin JL. Sonographic quantification of a hepato-renal index for the assessment of hepatic steatosis in comparison with 3T proton magnetic resonance spectroscopy. Eur J Gastroenterol Hepatol 2014;26(1):88-94.

Mehta NN, Yu Y, Saboury B, Foroughi N, Krishnamoorthy P, Raper A, et al. 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(9):1031-9.

Meshkani R, Adeli K. Hepatic insulin resistance, metabolic syndrome and cardiovascular disease. Clin Biochem 2009;42(13-14):1331-46.

Noguchi T, Nakao K, Asaumi Y, Morita Y, Otsuka F, Kataoka Y, et al. Noninvasive Coronary Plaque Imaging. J Atheroscler Thromb 2018;25(4):281-93.

Ogdie A, Grewal SK, Noe MH, Shin DB, Takeshita J, Chiesa Fuxench ZC, et al. Risk of Incident Liver Disease in Patients with Psoriasis, Psoriatic Arthritis, and Rheumatoid Arthritis: A Population-Based Study. J Invest Dermatol 2018;138(4):760-7.

Popa C, Netea MG, van Riel PL, van der Meer JW, Stalenhoef AF. The role of TNF-alpha in chronic inflammatory conditions, intermediary metabolism, and cardiovascular risk. J Lipid Res 2007;48(4):751-62.

Prussick RB, Miele L. Nonalcoholic fatty liver disease in patients with psoriasis: a consequence of systemic inflammatory burden? Br J Dermatol 2018;179(1):16-29.

Salahuddin T, Natarajan B, Playford MP, Joshi AA, Teague H, Masmoudi Y, et al. Cholesterol efflux capacity in humans with psoriasis is inversely related to non-calcified burden of coronary atherosclerosis. Eur Heart J 2015;36(39):2662-5.

Senn JJ, Klover PJ, Nowak IA, Mooney RA. Interleukin-6 induces cellular insulin resistance in hepatocytes. Diabetes 2002;51(12):3391-9.

Stefan N, Häring HU, Cusi K. Non-alcoholic fatty liver disease: causes, diagnosis, cardiometabolic consequences, and treatment strategies. Lancet Diabetes Endocrinol 2019;7(4):313-24.

Steinl DC, Kaufmann BA. Ultrasound imaging for risk assessment in atherosclerosis. Int J Mol Sci 2015;16(5):9749-69.

Tikkanen MJ, Fayyad R, Faergeman O, Olsson AG, Wun CC, Laskey R, et al. Effect of intensive lipid lowering with atorvastatin on cardiovascular outcomes in coronary heart disease patients with mild-to-moderate baseline elevations in alanine aminotransferase levels. Int J Cardiol 2013;168(4):3846-52.

van der Voort EA, Koehler EM, Dowlatshahi EA, Hofman A, Stricker BH, Janssen HL, et al. Psoriasis is independently associated with nonalcoholic fatty liver disease in patients 55 years old or older: Results from a population-based study. J Am Acad Dermatol 2014;70(3):517-24.

van Rosendael AR, Narula J, Lin FY, van den Hoogen IJ, Gianni U, Al Hussein Alawamlh O, et al. Association of High-Density Calcified 1K Plaque With Risk of Acute Coronary Syndrome. JAMA Cardiol 2020;5(3):282-90.

Webb M, Yeshua H, Zelber-Sagi S, Santo E, Brazowski E, Halpern Z, et al. Diagnostic value of a computerized hepatorenal index for sonographic quantification of liver steatosis. AJR Am J Roentgenol 2009;192(4):909-14.

Xia MF, Yan HM, He WY, Li XM, Li CL, Yao XZ, et al. Standardized ultrasound hepatic/renal ratio and hepatic attenuation rate to quantify liver fat content: an improvement method. Obesity (Silver Spring) 2012;20(2):444-52.
Younossi ZM. Non-alcoholic fatty liver disease - A global public health perspective. J Hepatol 2019;70(3):531-44.

Table 1. Comparison of Psoriasis Participants to Controls in the European Cohort

Parameter	Psoriasis	Controls	*P* Value
Clinical Characteristics	**N=76**	**N=76**	
Age, years	45 (12)	44 (11)	matched
Sex, m/f	53/23	55/21	matched
BMI, kg/m^2	29.7 (5.58)	28.2 (4.56)	matched
Waist circumference, cm	102 (13.8)	96.7 (13.5)	**0.048**
Low physical activity, n	9 (12)	11 (14)	0.78
Smoking, n	23 (30)	13 (17)	0.08
Hypertension, n	19 (25)	9 (12)	0.10
Dyslipidemia, n	26 (34)	13 (17)	**0.046**
Psoriasis Characteristics			
PASI score	12.8 (4.67)	-	-
Disease duration, years	18 (13)	-	-
BSA, %	15.7 (9.34)	-	-
Lab Values			
Alanine aminotransferase, U/L	27.3 (19.0)	27.3 (18.8)	1.0
Aspartate aminotransferase, U/L	23.3 (11.0)	22.8 (8.25)	0.83
C-reactive protein, mg/L	3.68 (4.11)	2.04 (1.38)	**0.01**
Glucose, mg/dL	98.3 (15.8)	94.5 (8.74)	0.14
Insulin, mcU/ml	16.94 (12.67)	11.1 (6.93)	
HOMA-IR	4.30 (3.53)	2.60 (2.00)	**0.005**
Lipid Profile			
Triglycerides, mg/dL	143 (88.2)	97.9 (41.3)	**0.002**
Total cholesterol, mg/dL	191 (31.9)	194 (36.9)	0.71
HDL cholesterol, mg/dL	50.7 (13.7)	56.9 (14.1)	**0.03**
LDL cholesterol, mg/dL	112 (28.1)	116 (33.5)	0.54
Fatty Liver Parameters			
NAFLD, n	46 (61)	34 (45)	**0.04**
SHRI	1.54 (0.46)	1.34 (0.39)	**0.02**
Atherosclerosis Characteristics			
Subclinical atherosclerosis, n	35 (46)	14 (18)	**<0.001**
Femoral atheroma plaques, n	32 (42)	11 (14)	**0.001**
Carotid atheroma plaques, n	15 (20)	9 (12)	0.21

BMI, Body mass index; PASI, Psoriasis area and severity index; BSA, body surface area; HOMA-IR, homeostatic model assessment for insulin resistance; HDL, high density lipoprotein; LDL, low density lipoprotein; NAFLD, non-alcoholic fatty liver disease; SHRI, sonographic hepatorenal index. Data are expressed as mean (standard deviation) for continuous variables and n (%) for categorical variables.

Table 2. Characteristics of Psoriasis Participants from European Cohort Stratified by NAFLD Status

Parameter	NAFLD Present	NAFLD Absent	*P* Value
Clinical Characteristics	**N=46**	**N=30**	
Age, years	47 (10)	42 (13)	0.09
Sex, m/f	33/13	20/10	0.64
BMI, kg/m^2	31.8 (5.26)	26.5 (4.50)	**<0.001**
Waist circumference, cm	107 (12.6)	93.8 (11.7)	**<0.001**
Low physical activity, n	9 (20)	0 (0)	**0.03**
Smoking, n	12 (26)	11(37)	0.30
Hypertension, n	15 (33)	4 (13)	0.78
Dyslipidemia, n	21 (46)	5 (17)	**0.04**
Psoriasis Characteristics			
PASI score	12.5 (3.31)	13.2 (6.24)	0.61
BSA, %	14.3 (6.36)	17.9 (12.4)	0.20
Disease duration, years	19 (13)	16 (10)	0.43
Lab Values			
Alanine aminotransferase, U/L	33 (21)	18 (11)	**0.002**
Aspartate aminotransferase, U/L	24 (8)	22 (14)	0.51
C-reactive protein, mg/L	3.97 (3.71)	3.18 (4.81)	0.52
Glucose, mg/dL	102 (18.6)	92.2 (7.27)	**0.01**
Insulin, mcU/ml	20.7 (14.4)	10.44 (3.86)	**<0.001**
HOMA-IR	5.40 (4.00)	2.40 (0.92)	**<0.001**
Lipid Profile			
Triglycerides, mg/dL	174 (95.4)	95.1 (46.3)	**<0.001**
Total cholesterol, mg/dL	199 (32.1)	179 (28.2)	**0.02**
HDL cholesterol, mg/dL	46.7 (11.3)	56.8 (15.0)	**0.009**
LDL cholesterol, mg/dL	119 (29.9)	103 (22.4)	**0.04**
Fatty Liver Parameters			
NAFLD, n	46	-	-
SHRI	1.84 (0.36)	1.10 (0.08)	**<0.001**
Atherosclerosis Characteristics			
Subclinical atherosclerosis, n	28 (61)	7 (23)	**0.006**
Femoral atheroma plaques, n	26 (57)	6 (20)	**0.008**
Carotid atheroma plaques, n	10 (22)	5 (17)	0.59

BMI; Body mass index. PASI; Psoriasis area and severity index. BSA; body surface area. HOMA-IR; homeostatic model assessment for insulin resistance. HDL; high density lipoprotein. LDL; low density lipoprotein. NAFLD; non-alcoholic fatty liver disease. SHRI; sonographic hepatorenal index. Data are expressed as mean (standard deviation) for continuous variables and n (%) for categorical variables.

Table 3. Comparison of Psoriasis Participants and Controls Stratified by NAFLD in the European Cohort

Parameter	Psoriasis with NAFLD	Psoriasis without NAFLD	Controls with NAFLD	Controls without NAFLD
Clinical Characteristics	**N=46**	**N=30**	**N=34**	**N=42**
Age, years	47.0 (9.96)	41.9 (13.1)	46.5 (10.5)	42.5 (11.9)
Sex, m/f	33/13	20/10	26/8	29/13
BMI, kg/m^2	31.8 (5.26) [a, c]	26.5 (4.50) [b, d]	30.3 (4.31) [a, c]	26.6 (4.19) [b, d]
Waist circumference, cm	107 (12.6) [a, c]	93.8 (11.7) [b, d]	102 (12.7) [a, c]	92.9 (12.7) [b, d]
Low physical activity, n	9 (20) [a]	0 (0) [b, d]	7 (21) [a]	4 (10)
Smoking, n	12 (26)	11(37)	5 (15)	8 (19)
Hypertension, n	15 (33) [c]	4 (13)	8 (24) [c]	1(2) [b, d]
Dyslipidemia, n	21 (46) [a, c]	5 (17) [d]	9 (26)	4 (10) [d]
Psoriasis Characteristics				
PASI score	12.5 (3.31)	13.2 (6.24)	-	-
Disease duration, years	18.7 (12.7)	16.3 (9.69)	-	-
BSA, %	14.3 (6.36)	17.9 (12.4)	-	-
Lab Values				
Alanine aminotransferase, U/L	33.1 (21.0) [a, c]	18.2 (10.6) [b, d]	33.8 (20.3) [a, c]	22.7 (16.9) [b, d]
Aspartate aminotransferase, U/L	24.1 (8.31)	22.0 (14.3)	24.5 (8.35)	21.8 (8.27)
C-reactive protein, mg/L	3.97 (3.71) [b, c]	3.18 (4.81) [b, c]	1.79 (1.05) [a, d]	2.23 (1.60) [a, d]
Glucose, mg/dL	102 (18.6) [a, c]	92.2 (7.27) [d]	96.8 (10.4)	92.9 (7.22) [d]
Insulin, mcU/ml	20.7 (14.4) [a. b, c]	10.44 (3.86) [d]	12.69 (8.89) [d]	9.98 (5.09) [d]
HOMA-IR	5.40 (4.00) [a, b, c]	2.40 (0.92) [d, c]	3.18 (2.69) [c, d]	1.87 (0.57) [a, d]
Lipid Profile				
Triglycerides, mg/dL	174 (95.4) [a, b, c]	95.1 (46.3) [d]	104 (44.6) [d]	92.5 (39.2) [d]
Total cholesterol, mg/dL	199 (32.1) [a]	179 (28.2) [d]	195 (38.3)	192 (36.9)
HDL cholesterol, mg/dL	46.7 (11.3) [a, c]	56.8 (15.0) [d]	52.8 (12.2)	60.1 (15.0) [d]
LDL cholesterol, mg/dL	119 (29.9) [a]	103 (22.4) [d]	116 (31.1)	115 (36.0)
Fatty Liver Parameters				
NAFLD, n	46	-	34	-
SHRI	1.84 (0.36) [a, b, c]	1.10 (0.08) [b, d]	1.66 (0.39) [a, c, d]	1.09 (0.09) [b, d]
Atherosclerosis Characteristics				
Subclinical atherosclerosis, n	28 (61) [a, b, c]	7 (23) [d, c]	11 (32) [c, d]	3 (7) [a, b, d]
Femoral atheroma plaques, n	26 (57) [a, b, c]	6 (20) [d]	8 (24) [d]	3 (7) [d]
Carotid atheroma plaques, n	10 (22) [c]	5 (17)	8 (24) [c]	1 (2) [b, d]

[a] $p<0.05$ vs. psoriasis without NAFLD; [b] $p<0.05$ vs. controls with NAFLD; [c] $p<0.05$ vs. controls without NAFLD; [d] $p<0.05$ vs. psoriasis with NAFLD.BMI, Body mass index; PASI, Psoriasis area and severity index; BSA, body surface area; HOMA-IR, homeostatic model assessment for insulin resistance; HDL, high density lipoprotein; LDL, low density lipoprotein; NAFLD, non-alcoholic fatty liver disease; SHRI, sonographic hepatorenal index. Data are expressed as mean (standard deviation) for continuous variables and n (%) for categorical variables.

Table 4. Characteristics of the United States Cohort Stratified by Maximum Hepatic ^{18}F-FDG Uptake

Parameter	Low Uptake N=81	High Uptake N=81	*P* Value
Clinical Characteristics			
Age, years	50 (14)	51 (12)	0.44
Sex, m/f	41/40	62/19	**<0.001**
BMI, kg/m^2	27.0 (4.36)	32.9 (6.36)	**<0.001**
Waist circumference, cm	93 (84-102)	106 (94-119)	**<0.001**
Current smoker, n	11 (14)	6 (7)	0.20
Hypertension, n	15 (19)	28 (35)	**0.02**
Hyperlipidemia, n	27 (33)	38 (47)	0.08
Diabetes, n	6 (7)	6 (7)	1.00
Lipid lowering medication, n	17 (21)	34 (42)	**0.004**
Metabolic syndrome, n	16 (20)	35 (45)	**<0.001**
Psoriasis Characteristics			
PASI score	5.6 (2.7-11)	6.7 (3.6-11)	0.18
BSA, %	4.6 (2.0-17)	6.8 (3.0-16)	0.26
Disease duration, years	18 (14)	22 (12)	0.07
Psoriatic arthritis, n	14 (17)	28 (35)	**0.01**
Clinical and Lab Values			
Alanine aminotransferase, U/L	24 (17-32)	27 (20-34)	0.07
Aspartate aminotransferase, U/L	20 (17-24)	21 (18-25)	0.12
hsC-reactive protein, mg/L	1.8 (0.71-3.1)	2.3 (0.80-4.3)	0.13
Glucose, mg/dL	94 (89-101)	99 (92-107)	**0.01**
Insulin, mcU/ml	9.5 (6.6-14)	14 (9.5-22)	**<0.001**
HOMA-IR	2.2 (1.5-3.3)	3.7 (2.3-5.3)	**<0.001**
Lipid Profile			
Triglycerides, mg/dL	92 (71-127)	110 (81-174)	**0.04**
Total cholesterol, mg/dL	171 (153-203)	176 (159-196)	0.99
HDL cholesterol, mg/dL	52 (46-70)	50 (40-59)	**0.01**
LDL cholesterol, mg/dL	95 (80-116)	106 (83-116)	0.34
Coronary Atherosclerosis Characteristics			
Total burden, mm^2 (x100)	1.1 (0.42)	1.4 (0.51)	**<0.001**
Non-calcified burden, mm^2 (x100)	1.0 (0.40)	1.3 (0.49)	**<0.001**
Fibrofatty burden, mm^2 (x100)	0.11 (0.087)	0.23 (0.15)	**<0.001**
Fibrous burden, mm^2 (x100)	0.90 (0.34)	1.0 (0.37)	**0.02**
Dense-calcified burden, mm^2 (x100)	0.07 (0.08)	0.04 (0.07)	**0.03**
Lipid rich necrotic core, mm^2	3.0 (1.7)	4.3 (2.3)	**<0.001**

High uptake defined as > the median uptake in the cohort (5.3 SUV). BMI; Body mass index. BSA; body surface area. AST; Aspartate aminotransferase. ALT; Alanine aminotransferase. HDL; High density lipoprotein. LDL; Low density lipoprotein. HOMA-IR; Homeostatic model assessment for insulin resistance. PASI; Psoriasis area severity index. Data are expressed as mean (standard deviation) or median (interquartile range) for continuous variables and n (%) for categorical variables.

Table 5. Association between Hepatic Steatosis, Hepatic Inflammation and Subclinical Atherosclerosis

5a) European cohort: Hepatic steatosis and subclinical atherosclerosis in participants with psoriasis and controls

	Psoriasis			Controls		
Exposures	OR	95% CI	*P* Value	OR	95% CI	*P* Value
SHRI	5.0	1.2-20	**0.02**	2.2	1.1-16	**0.02**
SHRI model 1	3.5	1.5-24	**0.01**	1.0	0.7-13	0.06

5b) United States cohort: Hepatic inflammation and subclinical atherosclerosis in psoriasis

	Noncalcified Burden		Fibrofatty Burden		Fibrous Burden		Lipid Rich Necrotic Core	
Exposures	Stand. β	*P* Value	Stand. β	*P* Value	Stand. β	*P* Value	Stand. β	*P* Value
Liver SUV_{max}	0.48	**<0.001**	0.62	**<0.001**	0.24	**0.003**	0.29	**<0.001**
Liver SUV_{max} model 1	0.28	**<0.001**	0.49	**<0.001**	0.02	0.84	0.28	**0.003**

Model 1 adjusted for age, sex, waist circumference, the homeostatic assessment for insulin resistance, systolic blood pressure, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, lipid-lowering therapy, c-reactive protein and current smoking. SHRI: Sonographic hepatorenal index. SUV: Standard uptake value.

Figure legends

Figure 1: Figure 1. Recruitment scheme of the European and United States cohorts.