Metabolic syndrome and its factors are associated with noncalcified coronary burden in psoriasis: An observational cohort study

Meron Teklu, BA,[a] Wunan Zhou, MD, MPH,[a] Promita Kapoor, CCRP,[a] Nidhi Patel, BS,[a] Amit K. Dey, MD,[a] Alexander V. Sorokin, MD, PhD,[a] Grigory A. Manyak, BA,[a] Heather L. Teague, PhD,[a] Julie A. Erb-Alvarez, MPH,[a] Aparna Sajja, MD,[b] Khaled M. Abdelrahman, BS,[a] Aarthi S. Reddy, BS,[a] Domingo E. Uceda, BS,[a] Sundus S. Lateef, BS,[a] Sujata M. Shanbhag, MD,[a] Colin Scott, BS,[a] Nina Prakash,[a] Maryia Svirydava, BS,[a] Philip Parel,[a] Justin A. Rodante, PA-C,[a] Andrew Keel, CRNP,[a] Evan L. Siegel, MD,[c] Marcus Y. Chen, MD,[a] David A. Bluemke, MD, PhD,[d] Martin P. Playford, PhD,[a] Joel M. Gelfand, MD, MSCE,[e,f] and Nehal N. Mehta, MD, MSCE, FAHA[a]

Bethesda, Baltimore, and Rockville, Maryland; Madison, Wisconsin; and Philadelphia, Pennsylvania

Background: Psoriasis is associated with a heightened risk of cardiovascular disease and higher prevalence of metabolic syndrome.

Objective: Investigate the effect of metabolic syndrome and its factors on early coronary artery disease assessed as noncalcified coronary burden by coronary computed tomography angiography in psoriasis.

Methods: This cross-sectional study consisted of 260 participants with psoriasis and coronary computed tomography angiography characterization. Metabolic syndrome was defined according to the harmonized International Diabetes Federation criteria.

Results: Of the 260 participants, 80 had metabolic syndrome (31%). The metabolic syndrome group had a higher burden of cardiometabolic disease, systemic inflammation, noncalcified coronary burden, and high-risk coronary plaque. After adjusting for Framingham risk score, lipid-lowering therapy, and biologic use, metabolic syndrome (β = .31; $P < .001$) and its individual factors of waist circumference (β = .33; $P < .001$), triglyceride levels (β = .17; P = .005), blood pressure (β = .18; P = .005), and fasting glucose (β = .17; P = .009) were significantly associated with noncalcified coronary burden. After adjusting for all other metabolic syndrome factors, blood pressure and waist circumference remained significantly associated with noncalcified coronary burden.

Limitations: Observational nature with limited ability to control for confounders.

From the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda[a]; Department of Internal Medicine, Johns Hopkins University Medical Center, Baltimore[b]; Department of Rheumatology, Arthritis and Rheumatism Associates, Rockville[c]; Department of Radiology, University of Wisconsin School of Medicine and Public Health, Madison[d]; and Department of Dermatology[e] and Department of Biostatistics, Epidemiology and Informatics,[f] Perelman School of Medicine, Philadelphia.

Funding sources: Supported by the National Heart, Lung, and Blood Institute Intramural Research Program (HL006193-07).

IRB approval status: Reviewed and approved by the institutional review board of the National Institutes of Health (approval 13H-0065).

Accepted for publication December 16, 2020.

Correspondence to: Nehal N. Mehta, MD, MSCE, FAHA, Lasker Senior Investigator, Section of Inflammation and Cardiometabolic Diseases, National Heart, Lung, and Blood Institute, National Institutes of Health, 10 Center Dr, Clinical Research Center, Room 5-5140, Bethesda, MD 20892. E-mail: nehal.mehta@nih.gov.

Published online February 3, 2021.

0190-9622

Published by Elsevier on behalf of the American Academy of Dermatology, Inc.

https://doi.org/10.1016/j.jaad.2020.12.044

Conclusions: In psoriasis, individuals with metabolic syndrome had more cardiovascular disease risk factors, systemic inflammation, and noncalcified coronary burden. Efforts to increase metabolic syndrome awareness in psoriasis should be undertaken to reduce the heightened cardiovascular disease risk. (J Am Acad Dermatol 2021;84:1329-38.)

Key words: atherosclerosis; cardiovascular disease; hypertension; metabolic syndrome; obesity; preventive medicine; psoriasis.

INTRODUCTION

Psoriasis is a chronic, inflammatory condition with important cardiometabolic consequences.[1] Psoriasis affects 2% to 3% of the adult population and is strongly associated with increased risk of cardiovascular disease and progression of atherosclerosis, making it feasible to study the longitudinal effects of chronic inflammation on cardiometabolic health.[1,2] The chronic inflammation observed in psoriasis is associated with a heightened prevalence of cardiovascular risk factors such as obesity, diabetes, hyperlipidemia, and hypertension, factors that compose the metabolic syndrome, a condition that is more prevalent in psoriasis patients than in the general population.[3,4] The International Diabetes Federation defines metabolic syndrome as meeting 3 or more of the following criteria: elevated waist circumference, triglycerides, blood pressure, and fasting glucose, as well as reduced high-density lipoprotein cholesterol.[5] Indeed, metabolic syndrome has independently been associated with advanced vascular damage, coronary heart disease, and mortality from all causes in noninflammatory populations,[6-8] partly driven by insulin resistance and endothelial dysfunction, which are associated with systemic inflammation.[9-12]

The interplay between central obesity and chronic inflammation may drive metabolic syndrome and other associated factors.[13-15] Specifically, excess visceral adipose tissue, through its ability to alter fatty acid metabolism and act as an endocrine organ that releases proinflammatory mediators, has been linked to and proposed as a causal factor for the metabolic derangements that encapsulate metabolic syndrome.[16-19] Excess visceral adipose tissue has been associated with increased risk of coronary artery disease in the general population and increased noncalcified coronary burden in psoriasis patients.[20-22] Despite its importance, visceral adipose tissue requires imaging-based analysis for quantification and is not an easily attainable factor in the clinical setting. It may be approximated by metabolic syndrome and its factors; however, to our knowledge, this has not yet been studied in psoriasis.

Coronary computed tomography angiography allows noninvasive assessment of early coronary artery disease through identification of plaque composition and characteristics beyond luminal stenosis.[23,24] Noncalcified plaque serves as an important predictor of future coronary artery disease events, especially in populations such as psoriasis patients, for whom traditional risk factors such as age and Framingham risk score are poorer predictors of cardiovascular disease.[25,26] Additionally, noncalcified coronary burden was recently found to be associated with cardiometabolic factors detected by machine learning in psoriasis[27] and may respond to pharmacologic therapy, making it an attractive target in reducing future cardiovascular disease events.[28,29] To our knowledge, there have been no studies evaluating the effect of metabolic syndrome and its factors on early vascular disease assessed as noncalcified coronary burden in psoriasis. Thus, in the present study, we aimed to characterize how metabolic syndrome in psoriasis affects cardiometabolic and cardiovascular disease risk factors, investigate the effect of metabolic syndrome and its individual factors on noncalcified coronary burden in psoriasis, and understand how metabolic syndrome and its factors are associated with directly measured visceral adipose tissue.

CAPSULE SUMMARY

- Psoriasis is associated with a higher prevalence of metabolic syndrome and risk of atherosclerosis.
- Metabolic syndrome and its factors, particularly hypertension and central obesity, are important determinants of noncalcified coronary burden in psoriasis. Increased awareness of metabolic syndrome in psoriasis is important to reduce this heightened cardiovascular disease risk.

METHODS

Study participants

The study participants were part of the Psoriasis, Atherosclerosis, and Cardiometabolic Disease Initiative, an ongoing longitudinal prospective study.

Abbreviations used:

GlycA: glycoprotein acetylation
IQR: interquartile range
SD: standard deviation

The study consisted of 336 consecutive participants with psoriasis who were aged 18 years or older and were recruited from January 1, 2013, through August 11, 2020, of whom 260 had coronary computed tomography angiography scans and adequate data for metabolic syndrome classification. Psoriasis was diagnosed by a certified dermatologist or rheumatologist according to typical skin findings, as well as systemic disease of the joints, nails, and hair. Psoriatic arthritis was diagnosed according to the Classification for Psoriatic Arthritis criteria by a certified rheumatologist. Exclusion criteria were an estimated glomerular filtration rate less than 30 mL/min/1.73 m^2, known current cardiovascular disease, and conditions that increase systemic inflammation such as internal solid or liquid malignancy within the past 5 years, HIV infection, any active infection 72 hours before, major surgery within the previous 3 months, current pregnancy, or lactation. The study protocol was approved by the institutional review board of the National Institutes of Health and complied with the Declaration of Helsinki.

Metabolic syndrome definition

Metabolic syndrome was defined as meeting 3 or more of the harmonized International Diabetes Federation criteria, which include (1) elevated waist circumference greater than 102 cm for men or greater than 88 cm for women; (2) triglyceride level greater than or equal to 150 mg/dL; (3) high-density lipoprotein C level less than 40 mg/dL for men or less than 50 mg/dL for women; (4) systolic blood pressure greater than or equal to 130 mm Hg, diastolic blood pressure greater than or equal to 85 mm Hg, or antihypertensive treatment in a patient with a history of hypertension; and (5) fasting glucose level greater than or equal to 100 mg/dL or drug treatment of elevated glucose level. In accordance with these criteria, all participants were given a binary metabolic syndrome score. A categorical score of 0 to 5 was also calculated for 239 participants with data for all 5 criteria available.

Clinical and laboratory measurements

Participants underwent measurements of routine vital signs, including waist circumference, and gave detailed histories. Psoriasis skin burden was determined with the Psoriasis Area Severity Index score. Systemic treatment included steroids and methotrexate, whereas biologic agents included tumor necrosis factor alpha, interleukin 12/23, and interleukin 17 inhibitors. Measurements of a fasting lipid panel, blood glucose, and inflammatory markers were performed. Lipoprotein subclass profiles along with glycoprotein acetylation (GlycA) were measured by an automated Vantera clinical nuclear magnetic resonance analyzer using the LipoProfile-3 algorithm (Labcorp).[30] High-density lipoprotein cholesterol efflux capacity was assessed according to previously described methods.[31]

Coronary burden characterization by coronary computed tomography angiography

All participants underwent coronary computed tomography angiography in the same scanner (320-detector row Aquilion ONE ViSION). Guidelines established by the NIH Radiation Exposure Committee were followed. Scans were performed with retrospective gating at 120 kV, tube current of 750 to 850 mA, and a gantry rotation time of less than or equal to 420 ms. Coronary artery characteristics across the main coronary arteries greater than 2 mm were phenotyped with QAngio CT (Medis) with high intraclass correlation coefficient (>0.95), using previously described methods.[32] Only clear deviations of the software's automatic contouring of lumen and outer wall segmentation were edited. Total, noncalcified, and dense calcified coronary artery burden were calculated by dividing the respective coronary artery volume by corresponding segment length and were subsequently adjusted for mean lumen intensity. Further analysis of high-risk plaque was defined as presence of either positive remodeling (a calculated index ≥1.1) or low-attenuation plaque (<30 Hounsfield units).[33]

Visceral and subcutaneous adipose tissue quantification

Participants underwent low-dose CT scans to quantify total, visceral, and subcutaneous adipose tissue volume (in cubic centimeters). Transverse slices (50-150) from the caudal end of the sternum to the cranial end of the pubic symphysis were interpreted with an automated software with a contour model algorithm, as previously described.[34,35] Visceral adipose tissue was defined as adipose tissue within the internal contour surrounding the abdominal cavity, and subcutaneous adiposity as adipose tissue found between the internal and external contour of the body. Slice adipose tissue volumes were averaged. Errors in configuration were screened and manually corrected by trained research

Table I. Baseline characteristics of the psoriasis cohort stratified by metabolic syndrome

Parameter	Entire cohort	MetSyn absent	MetSyn present	*P* value
Clinical characteristics	N = 260	N = 180	N = 80	
Age, y	50 (13)	48 (13)	52 (12)	**.04**
Sex, men	161 (62)	108 (60)	53 (66)	.34
Waist circumference, cm	97 (87-108)	92 (84-99.5)	110 (103-120)	**<.001**
Current smoker, no.	28 (11)	22 (12)	6 (8)	.26
Hypertension, no.	74 (28)	32 (18)	42 (53)	**<.001**
Diabetes, no.	19 (7)	8 (4)	11 (14)	**.008**
Hyperlipidemia, no.	99 (38)	59 (33)	40 (50)	**.008**
Lipid-lowering medication, no.	71 (27)	37 (21)	34 (43)	**<.001**
Hypertension treatment, no.	57 (22)	19 (11)	38 (48)	**<.001**
Diabetes treatment, no.	16 (6)	5 (3)	11 (14)	**<.001**
Psoriasis characteristics				
Psoriatic arthritis, no.	83 (32)	57 (32)	26 (33)	.89
PASI score	6.2 (3.0-10)	5.6 (3.0-9.0)	6.8 (3.2-13)	.07
Disease duration, y	20 (13)	20 (14)	22 (13)	.36
Topical treatment, no.	157 (60)	114 (63)	43 (54)	.14
Phototherapy, no.	27 (10)	16 (9)	11 (14)	.22
Nonbiologic systemic treatment, no.	33 (13)	20 (12)	13 (17)	.28
Biologic treatment, no.	74 (28)	47 (26)	27 (34)	.21
Clinical and laboratory values				
Systolic blood pressure, mm Hg	122 (113-130)	121 (112-128)	127 (114-137)	**.02**
Diastolic blood pressure, mm Hg	72 (67-78)	71 (67-77)	74 (67-83)	.06
hsC-reactive protein, mg/L	1.7 (0.80-3.6)	1.4 (0.70-3.1)	2.4 (0.90-4.6)	**.02**
GlycA, μmol/L	396 (352-446)	383 (344-444)	414 (370-450)	**.005**
HOMA-IR	2.6 (1.6-4.3)	2.0 (1.3-3.0)	4.8 (3.5-7.9)	**<.001**
Framingham risk score	2.0 (0.50-5.5)	1.5 (0.38-4.9)	4.0 (1.1-8.9)	**<.001**
Total adipose tissue, cc	34,384 (17,055)	28,560 (14,950)	47,099 (14,287)	**<.001**
Subcutaneous adipose tissue, cc	18,927 (10,969)	16,255 (10,376)	24,760 (9977)	**<.001**
Visceral adipose tissue, cc	15,457 (9266)	12,305 (7931)	22,339 (8219)	**<.001**
Lipid and lipoprotein profile				
Total cholesterol, mg/dL	181 (158-205)	182 (160-206)	181 (156-204)	.88
LDL cholesterol, mg/dL	102 (84-121)	104 (84.5-121)	99 (84-120)	.85
HDL cholesterol, mg/dL	52 (44-65)	58 (49-70)	44 (37-51)	**<.001**
Triglycerides, mg/dL	97 (70-141)	88 (65-116)	148 (100-201)	**<.001**
LDL particle number	1160 (891-1469)	1099 (861-1415)	1323 (1005-1592)	**.001**
HDL particle number	34.0 (30.5-38.7)	34.3 (31.0-39.6)	33.0 (29.6-37.0)	.08
VLDL particle number	42.4 (24.0-61.9)	39.8 (21.3-56.7)	48.6 (30.5-74.6)	**.003**
Small VLDL particle number	21.3 (12.2-33.0)	22.8 (13.9-34.7)	20.2 (8.40-26.9)	**.01**
Medium VLDL particle number	14.6 (5.75-26.3)	11.4 (4.10-22.6)	21.6 (9.10-42.6)	**<.001**
Large VLDL particle number	2.5 (1.2-5.0)	1.9 (0.90-3.3)	5.8 (3.0-12)	**<.001**
HDL cholesterol efflux capacity	0.95 (0.86-1.1)	0.98 (0.88-1.1)	0.91 (0.83-1.0)	**.002**
Coronary characteristics				
Presence of plaque, no.	87 (45)	51 (38)	36 (58)	**.01**
Presence of high-risk plaque, no.	40 (20)	21 (15)	19 (30)	**.02**
Total coronary burden, mm^2 ($\times$ 100)	1.2 (0.48)	1.1 (0.40)	1.5 (0.57)	**<.001**
Noncalcified coronary burden, mm^2 ($\times$ 100)	1.2 (0.46)	1.1 (0.37)	1.4 (0.56)	**<.001**
Dense-calcified coronary burden, mm^2 ($\times$ 100)	0.058 (0.12)	0.062 (0.13)	0.048 (0.079)	.39

Values are reported as mean (standard deviation) for parametric variables, median (interquartile range) for nonparametric continuous variables, and No. (%) for categorical variables. Coronary burden is presented as an average burden measured in the left anterior descending, left circumflex, and right coronary arteries, multiplied by a factor of 100.

Bolded *P* values are significant.

GlycA, Glycoprotein acetylation; *HDL*, high-density lipoprotein; *HOMA-IR*, homeostatic model assessment for insulin resistance; *LDL*, low-density lipoprotein; *MetSyn*, metabolic syndrome; *PASI*, Psoriasis Area Severity Index; *VLDL*, very low-density lipoprotein.

fellows with high intraclass correlation coefficient (0.98).

Statistical analysis

Values are reported as mean (standard deviation [SD]) for parametric variables, median (interquartile range [IQR]) for nonparametric variables, and number (%) for categorical variables. Statistical significance was assessed by Student *t*-test for parametric variables, Wilcoxon rank-sum test for nonparametric variables, and Pearson χ^2 test for categorical variables. Analysis of variance was used for multiple comparisons. Linear regressions were performed and a standardized β coefficient was reported. Adjusted variables included 10-year Framingham risk score, biologic use, and lipid-lowering therapy. $P < .05$ was considered significant. All analyses were performed with StataIC (version 16, StataCorp).

RESULTS

Characteristics of the study group

The cohort had a mean age of 50 years (SD 13), was predominantly composed of male patients (62%), and had body mass index characteristics consistent with an overweight profile (median 28.8; IQR 25.1-32.8). The cohort had mild to moderate skin disease severity as measured by the Psoriasis Area Severity Index score (median 6.2; IQR 3.0-10 kg/m^2) with psoriasis disease duration of 20 years (SD 13).

Characteristics of the study group stratified by metabolic syndrome status

Of the 260 participants with psoriasis, 80 met criteria for metabolic syndrome. Metabolic syndrome compared with no metabolic syndrome had no significant differences in Psoriasis Area Severity Index scores, disease duration, participants with psoriatic arthritis, or psoriasis-specific medication use. Individuals with metabolic syndrome were significantly older and more likely to have and be receiving treatment for hypertension, diabetes, and hyperlipidemia. The metabolic syndrome group had greater systemic inflammation by high-sensitivity C-reactive protein (median 2.4, IQR 0.90-4.6 mg/L vs median 1.4, IQR 0.70-3.1 mg/L; $P = .02$) and GlycA (median 414, IQR 370-450 μmol/L vs median 383, IQR 344-444 μmol/L; $P = .005$). Insulin resistance as assessed by the homeostatic model assessment for insulin resistance was higher in metabolic syndrome (median 4.8, IQR 3.5-7.9 vs median 2.0, IQR 1.3-3.0; $P < .001$). Despite having similar total cholesterol and low-density lipoprotein levels, participants with metabolic syndrome had lower high-density lipoprotein C levels (median 44, IQR 37-51 mg/dL vs median 58, IQR 49-70 mg/dL; $P < .001$), higher triglyceride levels (median 148, IQR 100-201 mg/dL vs median 88, IQR 65-116 mg/dL; $P < .001$), as well as higher low-density lipoprotein particle number (median 1323, IQR 1005-1592 vs median 1099, IQR 861-1415; $P = .001$) and higher very low-density lipoprotein particle number (median 48.6, IQR 30.5-74.6 vs median 39.8, IQR 21.3-56.7; $P = .003$). There was lower high-density lipoprotein cholesterol efflux capacity in metabolic syndrome (median 0.91, IQR 0.83-1.0 vs median 0.98, IQR 0.88-1.1; $P = .002$) (Table I).

Table II. Association between metabolic syndrome and coronary computed tomography angiography–based quantitative noncalcified coronary burden

	Unadjusted		Adjusted for FRS, biologic use, and lipid-lowering therapy	
Exposures	β	***P* value**	β	***P* value**
Binary MetSyn score	.36	**<.001**	.31	**<.001**
Categorical MetSyn score	.40	**<.001**	.33	**<.001**

Reported β is a standardized β for metabolic syndrome in each model, with the following standard deviations: binary MetSyn score = .46 and categorical MetSyn score = 1.4. Binary MetSyn score refers to the absent/present classification of metabolic syndrome. Categorical MetSyn score refers to the 0 to 5 metabolic syndrome score based on the number of criteria met. Bolded *P* values are significant.
FRS, Framingham risk score; *MetSyn*, metabolic syndrome.

Association between metabolic syndrome, its factors, and noncalcified coronary burden

In the participants with metabolic syndrome, there was a higher prevalence of coronary plaque (36 [58%] vs 51 [38%]; $P = .01$) and high-risk plaque (19 [30%] vs 21 [15%]; $P = .02$), with higher total (mean 1.5, SD 0.57 mm^2 vs mean 1.1, SD 0.40 mm^2; $P < .001$) and noncalcified burden (mean 1.4, SD 0.56 mm^2 vs mean 1.1, SD 0.37 mm^2; $P < .001$) (Table I). The presence of metabolic syndrome was significantly associated with higher noncalcified coronary burden ($\beta = .36$; $P < .001$), which persisted after adjusting for 10-year Framingham risk score, biologic use, and lipid-lowering therapy ($\beta = .31$; $P < .001$). The number of metabolic syndrome criteria met also associated with noncalcified coronary burden in unadjusted ($\beta = .40$;

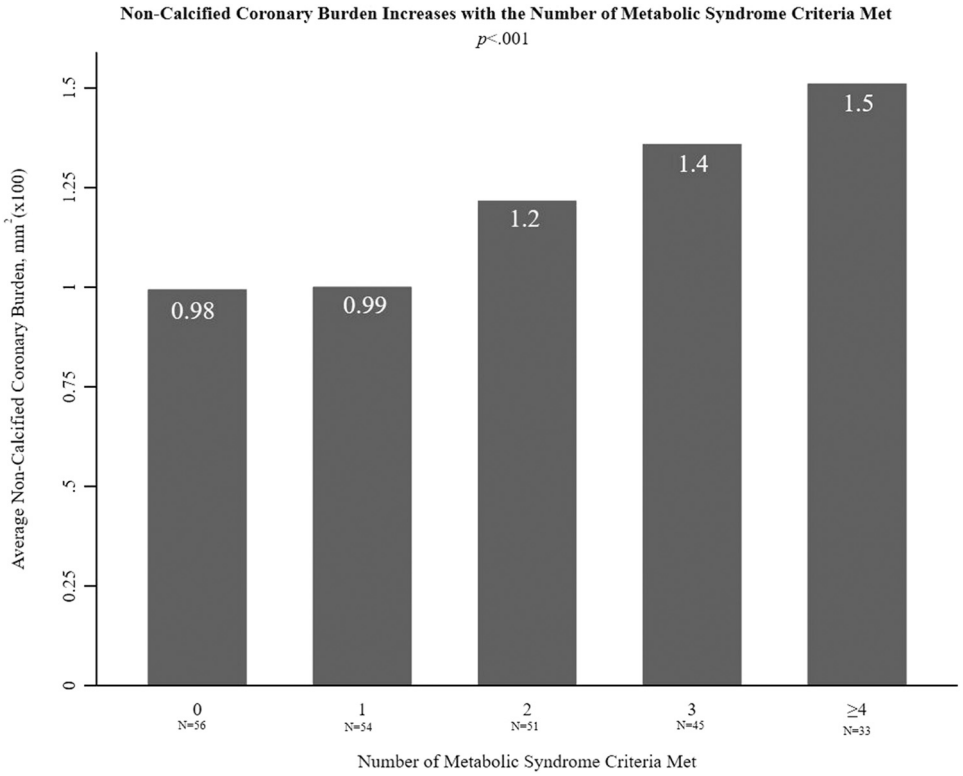

Fig 1. Average noncalcified burden by number of metabolic syndrome criteria met. Seven patients met 5 criteria and are combined with those who met 4 criteria. *P* value reported from analysis of variance.

Table III. Association between individual metabolic syndrome factors and coronary computed tomography angiography–based quantitative noncalcified coronary burden

	Unadjusted		Adjusted for FRS, biologic use, and lipid-lowering therapy		Adjusted for all binary MetSyn factors	
Binary exposures	β	***P* value**	β	***P* value**	β	***P* value**
Waist circumference criteria	.38	**<.001**	.33	**<.001**	.31	**<.001**
Triglycerides criteria	.21	**.001**	.17	**.005**	.12	.06
HDL criteria	.09	.16	.06	.32	-.07	.31
Blood pressure criteria	.26	**<.001**	.18	**.005**	.13	**.03**
Fasting glucose criteria	.26	**<.001**	.17	**.009**	.12	.06

Reported β is a standardized β for metabolic syndrome factors in each model, with the following standard deviations: waist circumference criteria = .50, triglycerides criteria = .41, high-density lipoprotein criteria = .40, blood pressure criteria = .50, and fasting glucose criteria = .49. Bolded *P* values are significant.
FRS, Framingham risk score; *HDL*, high-density lipoprotein; *MetSyn*, metabolic syndrome.

$P < .001$) and fully adjusted ($\beta = .33$; $P < .001$) models (Table II and Fig 1). When the 5 factors of metabolic syndrome were considered, the criteria for elevated waist circumference ($\beta = .33$; $P < .001$), triglycerides ($\beta = .17$; $P = .005$), blood pressure ($\beta = .18$; $P = .005$), and fasting glucose ($\beta = .17$; $P = .009$) were independently associated with noncalcified coronary burden after adjusting for each of the above-mentioned covariates. The criterion for reduced high-density lipoprotein C was not associated with noncalcified coronary burden. When all metabolic syndrome factors were adjusted for, the waist circumference ($\beta = .31$; $P < .001$) and blood pressure ($\beta = .13$; $P = .03$) criteria remained significantly associated with noncalcified coronary burden (Table III).

Table IV. Adjusted associations between metabolic syndrome, its individual factors, and quantitative measures of adiposity

	Visceral adipose tissue adjusted for FRS, biologic use, and lipid-lowering therapy		Subcutaneous adipose tissue adjusted for FRS, biologic use, and lipid-lowering therapy		Total adipose tissue adjusted for FRS, biologic use, and lipid-lowering therapy	
Exposures	β	***P* value**	β	***P* value**	β	***P* value**
Binary MetSyn score	.40	**<.001**	.36	**<.001**	.45	**<.001**
Categorical MetSyn score	.43	**<.001**	.54	**<.001**	.58	**<.001**
Waist circumference criteria	.43	**<.001**	.60	**<.001**	.62	**<.001**
Triglyceride criteria	.24	**<.001**	.12	.07	.21	**.001**
HDL criteria	.17	**.003**	.25	**<.001**	.26	**<.001**
Blood pressure criteria	.19	**.002**	.21	**.004**	.24	**.001**
Fasting glucose criteria	.23	**<.001**	.27	**<.001**	.30	**<.001**

Reported β is a standardized β for metabolic syndrome factors in each model, with the following standard deviations: binary MetSyn score = .46, categorical MetSyn score = 1.4, waist circumference criteria = .50, triglycerides criteria = .41, high-density lipoprotein criteria = .40, blood pressure criteria = .50, and fasting glucose criteria = .49. Binary MetSyn score refers to the absent/present classification of metabolic syndrome. Categorical MetSyn score refers to the 0 to 5 metabolic syndrome score based on the number of criteria met.
Bolded *P* values are significant.
FRS, Framingham risk score; *HDL*, high-density lipoprotein; *MetSyn*, metabolic syndrome.

Association between metabolic syndrome, its factors, and total, subcutaneous, and visceral adipose tissue volumes

Participants with metabolic syndrome had higher visceral (mean 22,339, SD 8219 cc vs mean 12,305, SD 7931 cc; $P < .001$), subcutaneous (mean 24,760, SD 9977 cc vs mean 16,255, SD 10,376 cc; $P < .001$), and total (mean 47,099, SD 14,287 cc vs mean 28,560, SD 14,950 cc; $P < .001$) adipose tissue volumes (Table I). Metabolic syndrome was associated with visceral, subcutaneous, and total adipose tissue volumes in unadjusted models (β = .50, .36, and .51, respectively; all $P < .001$) and models fully adjusted for Framingham risk score, biologic use, and lipid-lowering therapy (β = .40, .36, and .45, respectively; all $P < .001$). In fully adjusted models, the criteria for waist circumference (β = .43; $P < .001$), triglycerides (β = .24; $P < .001$), high-density lipoprotein (β = .17; P = .003), blood pressure (β = .19; P = .002), and fasting glucose (β = .23; $P < .001$) were associated with visceral adipose tissue (Table IV).

DISCUSSION

We performed a cross-sectional study to assess the effect of metabolic syndrome in a psoriasis cohort. Psoriasis participants with metabolic syndrome had elevated markers of systemic inflammation, insulin resistance, and an abnormal lipoprotein profile. Furthermore, individuals with metabolic syndrome had higher total, noncalcified, and high-risk coronary burden. Metabolic syndrome and its factors were significantly associated with noncalcified coronary burden in fully adjusted models. In models with all factors of metabolic syndrome adjusted for, blood pressure and waist circumference remained significantly associated with noncalcified coronary burden. Focusing on the central adiposity factor of metabolic syndrome, we further showed that metabolic syndrome and its factors were associated with visceral adipose tissue in fully adjusted models. Our findings collectively demonstrate the critical role of central adiposity in cardiovascular risk in psoriasis.

Metabolic syndrome affects approximately one-quarter of the adult population, with continued increasing prevalence.[36] Even considering how prevalent metabolic syndrome is in the general population, its prevalence is higher in individuals with psoriasis.[4,37] Metabolic syndrome and its defining metabolic derangements have devastating systemic consequences, including increased incidence of stroke, coronary heart disease, myocardial infarction, and cardiovascular disease mortality.[38,39] Psoriasis, in part owing to its associated increase in vascular and systemic inflammation, has been shown to not only increase but also accelerate atherosclerotic plaque formation.[1,40,41] Thus, understanding the influence of cardiovascular disease risk accelerators such as metabolic syndrome in psoriasis patients is of clinical importance. To our knowledge, this is the first study to show that metabolic syndrome and its factors are associated with higher noncalcified coronary burden in psoriasis. This relationship persisted after adjusting for traditional cardiovascular disease risk factors encompassed by the Framingham risk score, lipid-lowering therapy, and biologic use. When the factors of metabolic syndrome were compared, blood pressure and waist circumference emerged as especially important for noncalcified coronary burden. Hypertension is a

well-known cardiovascular disease risk factor, with inflammatory mediators such as T cells and cytokines known to play a role in its pathogenesis and eventual end-organ damage.[42] Patients with psoriasis have a higher risk of hypertension that increases with psoriasis severity.[43] Here, we showed that the hypertension factor of metabolic syndrome remains important to noncalcified coronary burden even when all other factors are controlled, indicating its importance as a marker of subclinical atherosclerosis in psoriasis patients independent of other traditional risk factors. Our study further highlights the importance of screening for and addressing the factors of metabolic syndrome in psoriasis patients, especially the factors relating to hypertension and central obesity.

Central adiposity is the most prevalent aspect of metabolic syndrome, with visceral adipose tissue playing a large role.[15,44] The significance of visceral adipose tissue to metabolic dysfunction and cardiovascular disease is well established, and our group has previously shown that visceral adipose tissue is strongly associated with noncalcified coronary burden in psoriasis.[20-22] Visceral adipose tissue is metabolically active and releases factors such as leptin, adiponectin, and inflammatory mediators and subsequently leads to increased systemic inflammation, hyperinsulinemia, glucose intolerance, and hypertriglyceridemia.[45-48] Although visceral adipose tissue is established as an important component of metabolic and cardiovascular risk in both the general population and psoriasis patients, its routine measurement in the clinical setting is not yet feasible. In this study, we showed that metabolic syndrome and its factors were strongly associated with visceral adipose tissue in psoriasis. Of the metabolic syndrome factors, waist circumference was most strongly associated with visceral adipose tissue. Waist circumference has been previously postulated as an inexpensive marker of visceral adiposity, although its association with total adiposity is stronger, a finding replicated in this study.[49,50] Although waist circumference and metabolic syndrome are not perfect markers of visceral adipose tissue quantity owing to their added relationship with subcutaneous and total adiposity, they did emerge as strongly associated with imaging-based quantitative visceral adipose tissue and noncalcified coronary burden in our psoriasis cohort. Given the inexpensive, noninvasive, and time-efficient nature of metabolic syndrome categorization, we believe metabolic syndrome and its factors, especially waist circumference, are important tools for estimating visceral adipose tissue and assessing risk of cardiometabolic and cardiovascular diseases in the clinical setting for patients with psoriasis.

The main limitation of this study is its observational and cross-sectional nature, which makes causality and directionality difficult to establish. Although our study provides strong evidence for higher noncalcified coronary burden in psoriasis patients with metabolic syndrome, further work on the role of inflammation and anti-inflammatory treatment on the effect of metabolic syndrome in psoriasis over time is needed. Additional work investigating differences in coronary plaque characteristics between psoriasis patients and the general population with metabolic syndrome is also warranted to better understand the role of chronic inflammation in metabolic syndrome.

In conclusion, individuals with psoriasis and metabolic syndrome had higher systemic inflammation, prevalence of cardiovascular disease risk factors, and noncalcified coronary burden. Efforts to increase metabolic syndrome awareness in psoriasis should be undertaken to reduce the associated heightened cardiovascular disease risk.

Conflicts of interest

Dr Siegel reports personal fees from AbbVie, Janssen, and Lilly outside the submitted work. Dr Gelfand reports personal fees from Abcentra, BMS, Boehringer Ingelheim, Cara (data safety monitoring board [DSMB]), GSK, Lilly (data monitoring committee), 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 Mehta is a full-time US government employee and has received research grants from AbbVie, Janssen, Novartis Corp, and Celgene outside the submitted work. Drs Zhou, Dey, Sorokin, Teague, Sajja, Shanbhag, Chen, Bluemke, and Playford, and Authors Teklu, Kapoor, Patel, Manyak, Erb-Alvarez, Abdelrahman, Reddy, Uceda, Lateef, Scott, Prakash, Svirydava, Parel, Rodante, and Keel have no conflicts of interest to declare.

REFERENCES

1. 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*. 2020;30(8):472-478.
2. Rachakonda TD, Schupp CW, Armstrong AW. Psoriasis prevalence among adults in the United States. *J Am Acad Dermatol*. 2014;70:512-516.
3. Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB, Gelfand JM. Prevalence of cardiovascular risk factors in patients with psoriasis. *J Am Acad Dermatol*. 2006;55(5):829-835.
4. 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. *Arch Dermatol*. 2011;147(4):419-424.
5. Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the

International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation*. 2009;120(16):1640-1645.
6. Lakka HM, Laaksonen DE, Lakka TA, et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA*. 2002;288(21):2709-2716.
7. Olijhoek JK, van der Graaf Y, Banga JD, Algra A, Rabelink TJ, Visseren FL. The metabolic syndrome is associated with advanced vascular damage in patients with coronary heart disease, stroke, peripheral arterial disease or abdominal aortic aneurysm. *Eur Heart J*. 2004;25(4):342-348.
8. Isomaa B, Almgren P, Tuomi T, et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care*. 2001;24(4):683-689.
9. Ridker PM, Buring JE, Cook NR, Rifai N. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events. *Circulation*. 2003;107(3):391-397.
10. Ridker PM. Clinical application of C-reactive protein for cardiovascular disease detection and prevention. *Circulation*. 2003;107(3):363-369.
11. Pasceri V, Willerson JT, Yeh ET. Direct proinflammatory effect of C-reactive protein on human endothelial cells. *Circulation*. 2000;102(18):2165-2168.
12. Festa A, D'Agostino R Jr, Howard G, Mykkänen L, Tracy RP, Haffner SM. Chronic subclinical inflammation as part of the insulin resistance syndrome: the Insulin Resistance Atherosclerosis Study (IRAS). *Circulation*. 2000;102(1):42-47.
13. Després JP. Is visceral obesity the cause of the metabolic syndrome? *Ann Med*. 2006;38(1):52-63.
14. El Brini O, Akhouayri O, Gamal A, Mesfioui A, Benazzouz B. Prevalence of metabolic syndrome and its components based on a harmonious definition among adults in Morocco. *Diabetes Metab Syndr Obes*. 2014;7:341-346.
15. Després JP, Lemieux I, Bergeron J, et al. Abdominal obesity and the metabolic syndrome: contribution to global cardiometabolic risk. *Arterioscler Thromb Vasc Biol*. 2008;28(6):1039-1049.
16. Kershaw EE, Flier JS. Adipose tissue as an endocrine organ. *J Clin Endocrinol Metab*. 2004;89(6):2548-2556.
17. Shah RV, Murthy VL, Abbasi SA, et al. Visceral adiposity and the risk of metabolic syndrome across body mass index: the MESA study. *JACC Cardiovasc Imaging*. 2014;7(12):1221-1235.
18. Lebovitz HE, Banerji MA. Point: visceral adiposity is causally related to insulin resistance. *Diabetes Care*. 2005;28(9):2322-2325.
19. Berg AH, Scherer PE. Adipose tissue, inflammation, and cardiovascular disease. *Circ Res*. 2005;96(9):939-949.
20. Neeland IJ, Turer AT, Ayers CR, et al. Body fat distribution and incident cardiovascular disease in obese adults. *J Am Coll Cardiol*. 2015;65(19):2150-2151.
21. Liu J, Fox CS, Hickson DA, et al. Impact of abdominal visceral and subcutaneous adipose tissue on cardiometabolic risk factors: the Jackson Heart Study. *J Clin Endocrinol Metab*. 2010;95(12):5419-5426.
22. Sajja A, Abdelrahman KM, Reddy AS, et al. Chronic inflammation in psoriasis promotes visceral adiposity associated with noncalcified coronary burden over time. *JCI Insight*. 2020;5(22):e142534.
23. 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.
24. Noguchi T, Nakao K, Asaumi Y, et al. Noninvasive coronary plaque imaging. *J Atheroscler Thromb*. 2018;25(4):281-293.
25. 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*. 2014;7(3):446-453.
26. 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*. 2015;240(1):197-204.
27. Munger E, Choi H, Dey AK, et al. Application of machine learning to determine top predictors of noncalcified coronary burden in psoriasis: an observational cohort study. *J Am Acad Dermatol*. 2020;83(6):1647-1653.
28. Lo J, Lu MT, Ihenachor EJ, et al. Effects of statin therapy on coronary artery plaque volume and high-risk plaque morphology in HIV-infected patients with subclinical atherosclerosis: a randomised, double-blind, placebo-controlled trial. *Lancet HIV*. 2015;2(2):e52-e63.
29. 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*. 2016;180:29-38.
30. Otvos JD, Mora S, Shalaurova I, Greenland P, Mackey RH, Goff DC Jr. Clinical implications of discordance between low-density lipoprotein cholesterol and particle number. *J Clin Lipidol*. 2011;5(2):105-113.
31. Mehta NN, Li R, Krishnamoorthy P, et al. Abnormal lipoprotein particles and cholesterol efflux capacity in patients with psoriasis. *Atherosclerosis*. 2012;224(1):218-221.
32. Salahuddin T, Natarajan B, Playford MP, 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):2662-2665.
33. Motoyama S, Ito H, Sarai M, et al. Plaque characterization by coronary computed tomography angiography and the likelihood of acute coronary events in mid-term follow-up. *J Am Coll Cardiol*. 2015;66(4):337-346.
34. Summers RM, Liu J, Sussman DL, et al. Association between visceral adiposity and colorectal polyps on CT colonography. *AJR Am J Roentgenol*. 2012;199(1):48-57.
35. Rivers JP, Powell-Wiley TM, Dey AK, et al. Visceral adiposity in psoriasis is associated with vascular inflammation by (18)F-fluorodeoxyglucose positron-emission tomography/computed tomography beyond cardiometabolic disease risk factors in an observational cohort study. *JACC Cardiovasc Imaging*. 2018;11(2 pt 2):349-357.
36. Mozumdar A, Liguori G. Persistent increase of prevalence of metabolic syndrome among U.S. adults: NHANES III to NHANES 1999-2006. *Diabetes Care*. 2011;34(1):216-219.
37. Langan SM, Seminara NM, Shin DB, et al. Prevalence of metabolic syndrome in patients with psoriasis: a population-based study in the United Kingdom. *J Invest Dermatol*. 2012;132(3 pt 1):556-562.
38. Butler J, Rodondi N, Zhu Y, et al. Metabolic syndrome and the risk of cardiovascular disease in older adults. *J Am Coll Cardiol*. 2006;47(8):1595-1602.
39. Galassi A, Reynolds K, He J. Metabolic syndrome and risk of cardiovascular disease: a meta-analysis. *Am J Med*. 2006;119(10):812-819.
40. Joshi AA, Lerman JB, Dey AK, et al. Association between aortic vascular inflammation and coronary artery plaque characteristics in psoriasis. *JAMA Cardiol*. 2018;3(10):949-956.

41. Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB. Risk of myocardial infarction in patients with psoriasis. *JAMA*. 2006;296(14):1735-1741.
42. Harrison DG, Guzik TJ, Lob HE, et al. Inflammation, immunity, and hypertension. *Hypertension*. 2011;57(2):132-140.
43. Duan X, Liu J, Mu Y, et al. A systematic review and meta-analysis of the association between psoriasis and hypertension with adjustment for covariates. *Medicine (Baltimore)*. 2020;99(9):e19303.
44. Després JP, Lemieux I. Abdominal obesity and metabolic syndrome. *Nature*. 2006;444(7121):881-887.
45. Wisse BE. The inflammatory syndrome: the role of adipose tissue cytokines in metabolic disorders linked to obesity. *J Am Soc Nephrol*. 2004;15(11):2792-2800.
46. Veilleux A, Caron-Jobin M, Noël S, Laberge PY, Tchernof A. Visceral adipocyte hypertrophy is associated with dyslipidemia independent of body composition and fat distribution in women. *Diabetes*. 2011;60(5):1504-1511.
47. Mathieu P, Poirier P, Pibarot P, Lemieux I, Després JP. Visceral obesity: the link among inflammation, hypertension, and cardiovascular disease. *Hypertension*. 2009;53(4):577-584.
48. Reneau J, Goldblatt M, Gould J, et al. Effect of adiposity on tissue-specific adiponectin secretion. *PLoS One*. 2018;13(6):e0198889.
49. Snijder MB, van Dam RM, Visser M, Seidell JC. What aspects of body fat are particularly hazardous and how do we measure them? *Int J Epidemiol*. 2006;35(1):83-92.
50. Ross R, Neeland IJ, Yamashita S, et al. Waist circumference as a vital sign in clinical practice: a consensus statement from the IAS and ICCR Working Group on Visceral Obesity. *Nat Rev Endocrinol*. 2020;16(3):177-189.