



Abdominal subcutaneous adipose tissue negatively associates with subclinical coronary artery disease in men with psoriasis

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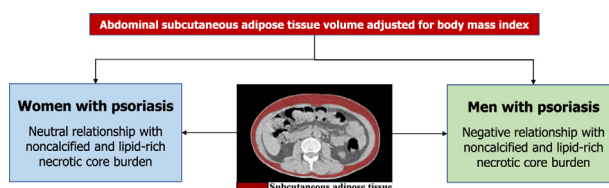
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GRAPHICAL ABSTRACT



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ABSTRACT

Objective: Understand the relationship between abdominal subcutaneous adipose tissue (ASAT) and coronary atherosclerosis defined as noncalcified and lipid-rich necrotic core burden in psoriasis.

Methods: We performed a cross-sectional study of 232 participants (92 women) with psoriasis and without known cardiovascular disease. Participants underwent coronary computed tomography angiography to characterize coronary atherosclerosis burden and low dose abdominal computed tomography to quantify subcutaneous and visceral adipose tissue. Fat depot volumes were first adjusted for each participant's BMI (ASAT_{adjBMI}).

Results: In women, there was a positive correlation between ASAT_{adjBMI} and systemic inflammation as assessed by hs-C-reactive protein ($r=0.30$; $p=.004$) and GlycA ($r=0.29$; $p=.007$) as well as total cholesterol ($r=0.24$; $p=.02$) and low-density lipoprotein cholesterol ($r=0.22$; $p=.04$). In men, ASAT_{adjBMI} correlated with hs-C-reactive protein ($r=0.18$; $p=.04$) and insulin resistance ($r=0.17$; $p=.04$). In models fully adjusted for traditional cardiovascular risk factors, ASAT_{adjBMI} negatively associated with noncalcified and lipid-rich necrotic core burden in men ($\beta=-0.17$; $p=.03$, $\beta=-0.20$; $p=.03$, respectively), but not women ($\beta=-0.06$; $p=.57$, $\beta=0.09$; $p=.49$, respectively) with psoriasis.

Conclusions: For a given BMI, ASAT negatively associated with coronary atherosclerosis burden in male participants with psoriasis. The observed sex-specific effects warrant further study of ASAT in states of chronic inflammation.

1. Introduction

Body fat distribution plays an important role in risk of cardiovascular disease [1]. While ectopic fat depots such as visceral, hepatic and epicardial adipose tissue have adverse cardiometabolic consequences,

subcutaneous adipose tissue (SAT), especially in the gluteo-femoral region, has been shown to have a protective effect [2-4]. This may be in part due to SAT's ability to act as a metabolic sink by providing a reservoir for excess energy storage [5]. The inability of this beneficial fat subtype to expand may lead to deposition of fat in metabolically unfa-

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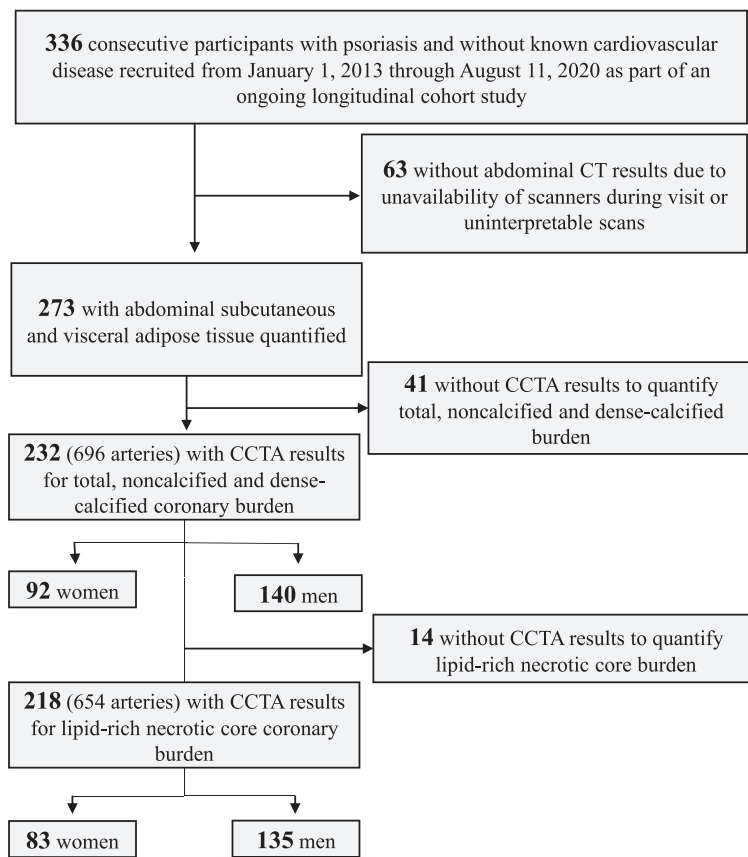


Fig. 1. Recruitment Scheme. CCTA; Coronary computed tomography angiography. CT; computed tomography.

avorable locations [6]. While the protective effect of gluteo-femoral SAT has been well studied, the role of abdominal subcutaneous adipose tissue (ASAT), especially as it relates to coronary atherosclerosis burden, is less explored. This is especially pertinent because of the clinical focus on abdominal adiposity, which in itself is a heterogeneous entity.

Increased abdominal adiposity has been associated with metabolic syndrome and incident cardiovascular events [7,8]. However, abdominal visceral adipose tissue has been postulated to be the main driver of these adverse consequences [9,10]. ASAT has fewer metabolic consequences than visceral fat and increasing ASAT has not been consistently associated with increasing cardiovascular risk factors [11,12]. Previous studies have reported lower arterial calcification and coronary plaque scores in those with higher ASAT [13-15]. However, there are limited data on whether ASAT may have a protective role in high-risk coronary atherosclerosis subtypes such as noncalcified and lipid-rich necrotic core burden.

Psoriasis is a chronic inflammatory condition associated with an increased risk of obesity and myocardial infarction than the general population [16,17]. Psoriasis and obesity are intimately linked through shared inflammatory pathways [18-20]. Obesity itself is a state of chronic low grade inflammation and adipocytes secrete proinflammatory mediators such as IL-6 and TNF-alpha which are major components of the pathophysiology of psoriasis [18,19]. The interaction between psoriasis and obesity makes this chronic inflammatory condition an interesting state to study the effects of fat depots on cardiovascular disease.

Coronary computed tomography angiography (CCTA) allows for non-invasive assessment of atherosclerosis burden and characterization of coronary phenotypes beyond luminal stenosis [21]. The differentiation of coronary atherosclerosis allows for identification of particularly high-risk phenotypes such as noncalcified and lipid-rich necrotic core burden [22-24]. Furthermore, CCTA derived factors such as noncalcified coronary burden not only associate with metabolic dysfunction in

psoriasis, but may be modifiable with statin and biologic therapies [25-27].

We therefore conducted a cross-sectional study of well-characterized participants with psoriasis and no known clinical cardiovascular disease to better understand the role ASAT may play in coronary atherosclerosis defined as noncalcified and lipid-rich necrotic core burden. In a sex stratified manner, we aimed to 1) elucidate the association between ASAT and cardiovascular risk factors in psoriasis, and 2) understand the relationship between ASAT and coronary atherosclerosis burden in participants with psoriasis.

2. Methods

2.1. Study participants

The study consisted of 336 consecutive participants with psoriasis 18 years or older recruited from January 1, 2013 through August 11, 2020, of whom 232 had CCTA results for coronary atherosclerosis burden characterization and low dose abdominal CT results for characterization of ASAT. All 232 participants had total, noncalcified and dense-calcified burden characterized and 218 had lipid-rich necrotic core burden characterized (Figure 1). Psoriasis was diagnosed by a certified dermatologist based on typical skin findings and systemic disease of the joints, nails, and hair. Exclusion criteria were an estimated glomerular filtration rate <30 mL/min/1.73 m², known current cardiovascular 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. The study protocol was approved by the institutional review board of the National Institutes of Health.

2.2. Clinical and laboratory measurements

Psoriasis skin burden was determined with the Psoriasis Area Severity Index (PASI) score. Biologic agents included TNF, IL-12/IL-23, and IL-17 inhibitors. Metabolic syndrome was defined according to the harmonized International Diabetes Federation criteria. Fasting glucose, insulin, lipids and inflammatory markers were measured. Insulin resistance was assessed by the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) calculated as (fasting glucose X fasting insulin)/405.

2.3. Coronary atherosclerosis burden characterization by CCTA

Participants underwent CCTA in the same scanner (320-detector row Aquilion ONE ViSION). Guidelines established by the National Institutes of Health Radiation Exposure Committee were followed. Scans were performed with retrospective gating at 120 kV, tube current of 750-850 mA and a gantry rotation time of ≤ 420 milliseconds. Noncalcified and dense calcified burden across the main coronary arteries > 2 mm diameter were analyzed using QAngio CT (Medis, The Netherlands) with high ICC (> 0.95). Clear deviations of the software's automatic contouring of lumen and outer wall segmentation were edited manually. Atherosclerosis volume was calculated as artery volume-lumen volume and atherosclerosis burden as sum of all atherosclerosis volumes/vessel length. Total, noncalcified and dense calcified burden were adjusted for mean lumen intensity. Maximum lipid rich necrotic core area was quantified for the three major coronary arteries with commercially available plaque quantification software (vascuCAP, Elucid Bioimaging Inc, Boston, MA) as previously described and did not require adjustment for mean lumen intensity [28].

2.4. Abdominal adipose tissue quantification

Participants underwent low dose CT scans to quantify visceral and subcutaneous adipose tissue volumes (cc). 100 transverse slices (50-150) from the caudal end of the sternum to the cranial end of the pubic symphysis were interpreted utilizing an automated software with a contour model algorithm. 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 fellows with high ICC (0.98).

2.5. Statistical analysis

Values are reported as mean (standard deviation) for parametric variables, median (interquartile range) for non-parametric variables, and n (%) for categorical variables. Statistical significance was assessed by Student's t-test for parametric variables, Wilcoxon rank-sum test for nonparametric variables, and Pearson's χ^2 test for categorical variables. Pearson correlations were performed. Abdominal subcutaneous and visceral adipose tissue volumes were first adjusted for body mass index (BMI) in a sex stratified manner. This was done by performing sex stratified linear regressions between abdominal adipose tissue markers and BMI, and the residual values were used for analyses. The residualized values were obtained by subtracting the observed values from the predicted values in the linear models. These BMI residualized values are henceforth referred to as "BMI adjusted" or "ASAT_{adjBMI}". Scatter plots and adjusted R^2 were used to check for fit of linear models. Adjusted covariates were based on clinical importance and included age, smoking status, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, diabetes status, systolic blood pressure, diastolic blood pressure, hypertension treatment, lipid-lowering therapy, biologic therapy, high-sensitivity c-reactive protein (hs-CRP), and BMI adjusted visceral adipose tissue volume. Missing data were excluded from

analyses. Standardized betas were reported for linear regression analyses. $P < .05$ was considered significant. All analyses were performed with StataIC 16 (Stata Corp., College Station, TX, USA).

3. Results

3.1. Comparison of participants included and excluded from analyses

Of the 336 participants initially enrolled in the study, 232 met criteria for inclusion. Those included did not significantly differ from those excluded in age (50 (13 years) vs 49 (13 years); $p = .42$), sex (40% women vs 38% women; $p = .71$), BMI (28.8 (25.2-32.9 kg/m²) vs 27.9 (24.6-32.3 kg/m²); $p = .33$) or percentage of participants with hypertension (29% vs 33%; $p = .41$), hyperlipidemia (41% vs 38%; $p = .64$), diabetes (8% vs 13%; $p = .15$) or use of lipid lowering therapy (29% vs 28%; $p = .73$).

3.2. Clinical characteristics of the cohort stratified by sex

Characteristics of the cohort stratified by sex are presented in Table 1. The women and men were similar in age and comorbidities such as hypertension, diabetes and hyperlipidemia. The men had higher 10-year Atherosclerotic Cardiovascular Disease risk scores (7.1 (6.1 %) vs 4.3 (4.1 %); $p = .001$) and fasting glucose levels (99 (92-105 mg/dL) vs 94 (87-103 mg/dL); $p = .005$). Psoriasis severity assessed by the PASI score, disease duration and biologic therapy did not significantly differ by sex. The men had lower total cholesterol levels (176 (157-197 mg/dL) vs 194 (161-220 mg/dL); $p = .008$) and lower HDL levels (50 (42-59 mg/dL) vs 62 (50-77 mg/dL); $p < .001$). Coronary atherosclerosis burden was higher in men for both noncalcified (1.3 (0.47 mm²) vs 0.96 (0.38 mm²); $p < .001$) and lipid-rich necrotic core (3.6 (2.6-5.1 mm²) vs 3.1 (2.2-4.0 mm²); $p = .002$) burden.

3.3. Measures of adiposity stratified by sex

While BMI did not differ by sex, the men had higher waist circumferences (102 (93-111 cm) vs 89 (80-103 cm); $p < .001$), waist-to-hip ratios (0.99 (0.94-1.0) vs 0.90 (0.85-0.94); $p < .001$) and unadjusted visceral adipose tissue volumes (18798 (9048 cc) vs 10543 (6985 cc); $p < .001$). However, the men had lower unadjusted subcutaneous adipose tissue volumes (17018 (9965 cc) vs 22717 (12228 cc); $p < .001$).

3.4. Sex stratified correlations between ASAT_{adjBMI} and cardiovascular risk factors

Correlations between ASAT_{adjBMI} and cardiovascular risk factors are presented in Table 2. In women, ASAT_{adjBMI} positively correlated with hs-CRP ($r = 0.30$; $p = .004$), GlycA ($r = 0.29$; $p = .007$), total cholesterol ($r = 0.24$; $p = .02$) and LDL cholesterol ($r = 0.22$; $p = .04$). In men, there was a weaker relationship compared to women with hs-CRP ($r = 0.18$; $p = .04$) and a positive relationship with insulin resistance ($r = 0.17$; $p = .04$) assessed by HOMA-IR. In both sexes, there was a mild nonsignificant negative correlation with diastolic blood pressure ($r = -0.18$; $p = .09$ for women and $r = -0.10$; $p = .23$ for men). While the raw ASAT volume positively correlated with the raw visceral adipose tissue volume in women ($r = 0.67$; $p < .001$) and men ($r = 0.59$; $p < .001$), ASAT_{adjBMI} did not significantly correlate with BMI adjusted visceral adipose tissue volume in women ($r = 0.10$; $p = .37$), but negatively correlated with this fat depot in men ($r = -0.18$; $p = .04$).

3.5. Association between ASAT_{adjBMI} and coronary atherosclerosis burden stratified by sex

Sex stratified associations between ASAT_{adjBMI} and coronary atherosclerosis burden are presented in Table 3. The standard deviation for ASAT_{adjBMI} was 6260 cc for women and 5175 cc for men.

Table 1
Characteristics of the cohort stratified by sex

Parameter	Women n=92	Men n=140	P value
Age, years	49 (14)	51 (12)	0.44
Current smoker, n	15 (16)	12 (9)	0.07
Hypertension, n	29 (32)	38 (27)	0.47
Diabetes, n	9 (10)	9 (6)	0.35
Hyperlipidemia, n	33 (36)	62 (44)	0.20
Lipid-lowering medication, n	15 (16)	53 (38)	<0.001
Hypertension treatment, n	23 (25)	30 (21)	0.53
Diabetes treatment, n	8 (9)	7 (5)	0.26
Metabolic syndrome, n	24 (28)	47 (34)	0.33
10-year ASCVD risk, %	4.3 (4.1)	7.1 (6.1)	0.001
Systolic blood pressure, mm Hg	122 (112-129)	123 (113-132)	0.51
Diastolic blood pressure, mm Hg	71 (66-77)	73 (67-79)	0.10
hsC-reactive protein, mg/L	2.2 (0.90-5.0)	1.6 (0.70-3.1)	0.04
GlycA, μ mol/L	41.3 (76.2)	40.3 (66.3)	0.30
Glucose, mg/dL	94 (87-103)	99 (92-105)	0.005
Insulin, mcU/ml	11 (7.2-16)	11 (7.0-19)	0.42
HOMA-IR	2.5 (1.6-4.3)	2.7 (1.6-4.7)	0.35
Measures of Adiposity			
Body mass index, kg/m ²	28.6 (24.4-33.2)	28.8 (25.6-32.6)	0.51
Waist circumference, cm	89 (80-103)	102 (93-111)	<0.001
Waist-to-hip ratio	0.90 (0.85-0.94)	0.99 (0.94-1.0)	<0.001
Total adipose tissue, cc	33260 (17679)	35816 (16940)	0.27
Subcutaneous adipose tissue, cc	22717 (12228)	17018 (9965)	<0.001
Visceral adipose tissue, cc	10543 (6985)	18798 (9048)	<0.001
Psoriasis Characteristics			
PASI score	5.4 (2.7-7.7)	6.4 (3-11.9)	0.07
Disease duration, years	19 (14)	20 (13)	0.77
Biologic treatment, n	34 (37)	36 (26)	0.07
Lipid Profile			
Total cholesterol, mg/dL	194 (161-220)	176 (157-197)	0.008
LDL cholesterol, mg/dL	105 (85-128)	102 (84-120)	0.47
HDL cholesterol, mg/dL	62 (50-77)	50 (42-59)	<0.001
Triglycerides, mg/dL	104 (70-137)	98 (75-147)	0.60
Coronary Characteristics			
Total burden, mm ² (x100)	1.0 (0.36)	1.4 (0.50)	<0.001
Noncalcified burden, mm ² (x100)	0.96 (0.38)	1.3 (0.47)	<0.001
Dense-calcified burden, mm ² (x100)	0.05 (0.05)	0.06 (0.10)	0.20
Lipid rich necrotic core, mm ²	3.1 (2.2-4.0)	3.6 (2.6-5.1)	0.002

Values reported as mean (SD) for parametric variables, median (IQR) for non-parametric continuous variables, and n (%) for categorical variables. ASCVD; Atherosclerotic Cardiovascular Disease. HOMA-IR; homeostatic model assessment for insulin resistance. PASI; psoriasis area severity index. LDL; low-density lipoprotein. HDL; high-density lipoprotein.

Table 2
Associations between ASAT_{adjBMI} and cardiovascular risk parameters stratified by sex

Parameter	Women N=92		Men N=140	
	r	P Value	r	P Value
10-year ASCVD risk, %	0.06	0.66	0.04	0.65
Systolic blood pressure, mm Hg	-0.03	0.77	-0.02	0.79
Diastolic blood pressure, mm Hg	-0.18	0.09	-0.10	0.23
hsC-reactive protein, mg/L	0.30	0.004	0.18	0.04
GlycA, μ mol/L	0.29	0.007	0.04	0.61
Glucose, mg/dL	0.06	0.56	0.11	0.20
Insulin, mcU/ml	0.01	0.91	0.15	0.07
HOMA-IR	-0.02	0.86	0.17	0.04
Total cholesterol, mg/dL	0.24	0.02	-0.05	0.58
LDL cholesterol, mg/dL	0.22	0.04	-0.06	0.49
HDL cholesterol, mg/dL	0.12	0.27	-0.04	0.63
Triglycerides, mg/dL	0.03	0.74	0.04	0.65
VAT _{adjBMI}	0.10	0.37	-0.18	0.04

Pearson correlation between body mass index adjusted subcutaneous adipose tissue volume and traditional cardiovascular risk factors. ASAT_{adjBMI}; abdominal subcutaneous adipose tissue adjusted for body mass index. ASCVD; Atherosclerotic Cardiovascular Disease. HOMA-IR; homeostatic model assessment for insulin resistance. LDL; low density lipoprotein. HDL; high density lipoprotein. VAT_{adjBMI}; visceral adipose tissue volume adjusted for body mass index.

In the women with psoriasis, there was no significant relationship between ASAT_{adjBMI} and noncalcified or lipid-rich necrotic core burden in models that were unadjusted ($\beta=0.04$; $p=.72$, $\beta=0.04$; $p=.69$, respectively), adjusted for traditional risk factors encompassed by age, smoking status, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, diabetes status, systolic blood pressure, diastolic blood pressure, hypertension treatment, lipid-lowering therapy, biologic therapy, and high-sensitivity c-reactive protein ($\beta=-0.06$; $p=.57$, $\beta=0.09$; $p=.49$, respectively), or adjusted for traditional risk factors plus BMI adjusted visceral adipose tissue volume ($\beta=-0.06$; $p=.56$, $\beta=0.09$; $p=.48$, respectively). However, in the men, there was a negative association between ASAT_{adjBMI} and noncalcified and lipid-rich necrotic core burden ($\beta=-0.18$; $p=.04$, $\beta=-0.22$; $p=.01$, respectively). These negative relationships persisted after adjusting for traditional cardiovascular risk factors ($\beta=-0.17$; $p=.03$, $\beta=-0.20$; $p=.03$, respectively) and BMI adjusted visceral adipose tissue volume ($\beta=-0.17$; $p=.03$, $\beta=-0.20$; $p=.03$, respectively). These relationships were similar for total burden, which is the sum of all atherosclerosis subtypes, though it did not meet significance for the men or women of the cohort.

4. Discussion

In this cross-sectional study, we showed differential association of ASAT_{adjBMI} with traditional cardiovascular risk factors in men and women with psoriasis. In men, higher ASAT_{adjBMI} correlated posi-

Table 3
Sex stratified associations between ASAT_{adjBMI} and coronary atherosclerosis burden

	Noncalcified burden				Lipid-rich necrotic core burden			
	Women		Men		Women		Men	
	Stand. β	P Value	Stand. β	P Value	Stand. β	P Value	Stand. β	P Value
Unadjusted	0.04	0.72	-0.18	0.04	0.04	0.69	-0.22	0.01
Model 1	-0.06	0.57	-0.17	0.03	0.09	0.49	-0.20	0.03
Model 1 + VAT _{adjBMI}	-0.06	0.56	-0.17	0.03	0.09	0.48	-0.20	0.03

Standard deviations for interpreting standardized betas are as follows: ASAT_{adjBMI}; 6260 cc for women and 5175 cc for men; Noncalcified burden; 0.38 for women and 0.47 for men; lipid-rich necrotic core; 1.9 for women and 2.4 for men. Model 1: Adjusted for age, smoking status, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, diabetes status, systolic blood pressure, diastolic blood pressure, hypertension treatment, lipid-lowering therapy, biologic therapy, high-sensitivity c-reactive protein. ASAT_{adjBMI}; abdominal subcutaneous adipose tissue adjusted for body mass index. VAT_{adjBMI}; visceral adipose tissue adjusted for body mass index.

tively with insulin resistance and negatively with BMI adjusted visceral adipose tissue volume while women had a stronger positive correlation with markers of systemic inflammation, total cholesterol and LDL cholesterol. This SAT volume negatively associated with non-calcified and lipid-rich necrotic core coronary burden independent of traditional cardiovascular risk factors, systemic inflammation and BMI adjusted visceral adipose tissue volume in men, but not women, with psoriasis. Taken together, these findings suggest a possible atheroprotective effect of ASAT volume for a given BMI in men with psoriasis. Furthermore, they contribute to the body of literature establishing adipose tissue as a heterogeneous entity and highlight the need for further work elucidating the role of abdominal subcutaneous adipose tissue in cardiovascular disease risk.

Psoriasis affects about 1-9% of the population based on geographical location and is associated with an increased risk of cardiovascular disease [17,29]. Obesity may be a risk factor for psoriasis and psoriasis may promote obesity [30-32]. Psoriasis and obesity share inflammatory pathways related to T helper cells, TNF α , and IL-6, and the adipokines leptin and resistin have consistently been shown to be elevated in patients with psoriasis [18,19,33,34]. Thus, understanding the effects of fat depots in patients with psoriasis is of particular importance. While increased abdominal adiposity has generally been associated with adverse cardiovascular outcomes, non-invasive imaging modalities have allowed differentiation of this depot into visceral and subcutaneous compartments [7]. Visceral adipose tissue associates with metabolic dysfunction and atherosclerosis both in the general population and psoriasis [15,25,35]. The role of ASAT, especially as it relates to coronary atherosclerosis burden characteristics is less explored. Previous studies have shown that ASAT may not associate or associate negatively with cardiovascular risk factors [11,12]. ASAT may also associate with lower arterial calcification and plaque scores, however, the relationship between ASAT and high-risk coronary atherosclerosis burden requires further study [13,14]. Here, we show that for a given BMI, higher ASAT negatively associated with coronary atherosclerosis defined as noncalcified and lipid-rich necrotic core burden in a sex specific manner. Noncalcified, lipid-rich plaques are more rupture prone and important harbingers of future coronary artery disease events, making them important phenotypes for preventative measures [22,24]. Furthermore, in states of chronic inflammation such as psoriasis, cardiovascular disease risk is accelerated and traditional risk factors such as age provide poorer assessment of risk. Therefore, quantification of coronary atherosclerosis burden can be especially vital [17,36].

One proposed mechanism for the protective effect of SAT is its ability to act as a metabolic sink and therefore a physiologic storage space in states of excess energy [5]. A decrease in this reservoir is hypothesized to play a role in formation of ectopic fat depots such as visceral adipose tissue [6]. States of lipodystrophy, in which SAT depots are depleted and adipose tissue accumulates in foreign regions, strengthen this hypothesis [37]. Mouse studies involving intra-abdominal transplantation

of SAT have shown improvement in glucose tolerance [38]. One mechanism for the improved insulin sensitivity seen on thiazolidinediones may be their ability to specifically increase SAT volume [39,40]. Our work adds to this body of literature supporting SAT as a protective marker by uniquely demonstrating a possible protective role of ASAT on coronary atherosclerosis burden in a high-risk population in a sex dependent manner. In our cohort, ASAT had a stronger positive relationship with systemic inflammation, total cholesterol and LDL cholesterol in women accompanied by no significant relationship with coronary atherosclerosis burden. On the other hand, men's ASAT positively associated with insulin resistance and negatively associated with BMI adjusted visceral adipose tissue volume and coronary atherosclerosis burden. These findings suggest possible differential effects of ASAT by sex in this chronically inflamed population. While the observational nature and small sample size of this study do not allow for establishing a mechanism for the observed sex differences in the association between ASAT_{adjBMI} and high-risk coronary atherosclerosis burden, the differential associations seen with cardiovascular risk factors by sex may serve as a possible explanation and should be explored further. Notably, the negative association seen between ASAT_{adjBMI} and BMI adjusted visceral adipose tissue volume uniquely in the men of this cohort may point to sex differences in the interplay between ASAT and visceral adipose tissue. Though the exact mechanism is not yet established, previous studies have also reported sex differences in the impact of SAT on cardiovascular risk factors [3,12]. Furthermore, there are reported differences in cellularity, gene expression, innervation and hormonal effects of SAT between men and women [41-44]. Though not quantified in this study, differentiation of ASAT into deep and superficial depots may clarify these results, as deep ASAT may behave similarly to visceral adipose tissue [45,46]. Future studies assessing the histological and genetic features of ASAT stratified by sex in psoriasis are warranted.

The main limitations of this study include its small sample size, small effect size, and observational nature which makes causality and directionality difficult to establish. Furthermore, we do not differentiate between deep and superficial ASAT and further work assessing if the protective effects persist with differentiation of these fat depots is necessary. In addition, the observed sex differences need elucidation in a larger cohort and in studies where ASAT biopsies are performed in chronically inflamed patients. Finally, these results require validation in larger and longitudinal studies with cardiovascular events data.

5. Conclusions

In a well phenotyped cohort of participants with psoriasis, we showed that for a given BMI, higher ASAT volume negatively associated with coronary atherosclerosis defined as noncalcified and lipid-rich necrotic core burden in men with psoriasis. These results propose ASAT as a possible protective marker of coronary atherosclerosis in male patients with psoriasis, adding to the body of literature proposing adipose tissue as a heterogeneous entity. In the clinical setting, our findings high-

light the importance of differentiating total adiposity into specific fat depots, which may allow for better understanding of cardiovascular risk. The observed sex-specific effects warrant further study of ASAT in states of chronic inflammation.

Data availability statement

Written data requests can be made to the corresponding author.

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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. Khera has served as a scientific advisor to Sanofi, Medicines Company, Maze Therapeutics, Navigator Pharmaceuticals, Sarepta Therapeutics, Verve Therapeutics, Amgen, Color, and Columbia University (NIH); received speaking fees from Illumina, MedGenome, Amgen, and the Novartis Institute for Biomedical Research; received sponsored research agreements from the Novartis Institute for Biomedical Research and IBM Research. All other authors report no conflicts of interest.

Author contributions

MT, WZ and NNM conceived, carried out the study and performed the analyses. MT, PK, NP, MPP, AVS, AKD, HLT, GAM, JAR, AK and MYC performed data acquisition and analyses. All authors were involved in writing the paper and had final approval of the submitted and published versions.

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