Characterization of Lipoprotein Composition and Function in Pediatric Psoriasis Reveals a More Atherogenic Profile

Wynnis L. Tom, MD[1], **Martin P. Playford, PhD**[2], **Shehla Admani, MD**[1], **Balaji Natarajan, MD**[2], **Aditya A. Joshi, MD**[2], **Lawrence F. Eichenfield, MD**[1,*], and **Nehal N. Mehta, MD**[2,*]

[1]Departments of Pediatrics and Medicine (Dermatology), University of California, San Diego and Rady Children's Hospital, San Diego, CA

[2]Cardiology Branch, National Institutes of Health, Bethesda, MD

Abstract

Psoriasis is associated with increased cardiovascular disease (CVD) in adults, but the risk profile of children with psoriasis remains to be fully characterized. We measured lipoprotein composition and function in 44 pediatric psoriasis patients and 44 age- and sex-matched healthy controls, using NMR spectroscopy and a validated *ex vivo* assay of high density lipoprotein (HDL) cholesterol efflux capacity (CEC). Mean age was 13.0 years and the population was ethnically diverse. Children with psoriasis had higher waist-hip ratios (0.85 vs. 0.80; p<0.002) and insulin resistance measures (log transformed HOMA-IR 0.65 vs. 0.41; p=0.07). Despite comparable traditional lipid values, having psoriasis was associated with higher apolipoprotein B concentrations (72.4 vs. 64.6; p=0.02), decreased large HDL particles (5.3 vs. 6.7; p<0.01), and reduced CEC after adjusting for age, sex, fasting glucose, HOMA-IR, systolic blood pressure, body mass index, apolipoprotein A-1, and HDL cholesterol concentration (beta -0.22, p=0.02). Pediatric psoriasis patients have a more atherogenic cardiometabolic risk profile, with evidence of insulin resistance and lipoprotein dysfunction by particle size, number, and functional assessment. These findings may provide a basis for the observed link later in life between psoriasis and CVD and support the need to screen and educate young patients to minimize later complications.

Address for correspondence: Wynnis L. Tom, MD, Pediatric & Adolescent Dermatology, University of California, San Diego/Rady Children's Hospital, 8010 Frost Street, Suite 602, San Diego, CA 92123, Phone: 858-966-6795, Fax: 858-966-4040, wtom@rchsd.org.
*denotes equal contribution

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Introduction

Psoriasis is a chronic, immune-mediated skin disorder with an established association with increased metabolic and cardiovascular disease (CVD) risk in adults (Armstrong *et al.*, 2013; Langan *et al.*, 2012; Samarasekera *et al.*, 2013). Mechanisms linking these conditions remain to be fully understood, but systemic inflammation in psoriasis appears to predispose to abnormalities that include a pro-atherogenic lipoprotein profile, large vessel inflammation, and adipokine dysregulation (Li *et al.*, 2014; Mehta *et al.*, 2012; Mehta *et al.*, 2011; Rajappa *et al.*, 2015). As psoriatic disease begins in childhood in approximately one-third of cases, the potential for early impairment is of interest. Several studies have demonstrated that obesity, insulin resistance, and dyslipidemia are present at higher rates in affected children (Augustin *et al.*, 2010; Ferretti *et al.*, 1993; Koebnick *et al.*, 2011; Paller *et al.*, 2013; Torres *et al.*, 2014), but additional study is needed on the timing, magnitude, and factors influencing and underlying such dysfunction.

To further characterize cardiometabolic risk in affected children, detailed lipoprotein characterization was performed with comparison to healthy controls. Beyond traditional lipid concentration, nuclear magnetic resonance (NMR) spectroscopy can accurately detect lipoprotein particle composition, size, and number (Otvos *et al.*, 1992). In particular, this includes low density lipoprotein (LDL) particle concentration (LDL-p), which has recently been shown to be a superior marker of CVD risk to LDL cholesterol concentration (LDL-c), particularly when the two values are discordant (Cromwell *et al.*, 2007; Otvos *et al.*, 2011; Rizzo *et al.*, 2013). High density lipoprotein (HDL) particle composition and size can also be assessed, which have been shown to be altered and related to vascular inflammation in adult psoriasis (Holzer *et al.*, 2012; Yu *et al.*, 2012).

A key function of HDL is transportation of cholesterol from peripheral tissues, such as the arterial wall, to the liver for excretion into the bile. We and others have utilized a reliable assay to estimate this important property of HDL-promoted cholesterol efflux capacity (CEC), which may be more significant than traditional HDL cholesterol concentration (HDL-c) in predicting risk of CVD (Khera *et al.*, 2011; Khera and Rader, 2013; Rohatgi *et al.*, 2014). These advanced measures of lipoprotein composition and function may be useful for early detection of cardiometabolic aberrations in the pediatric population, where changes are likely to be more subtle. We hypothesized that psoriasis in children would promote a more atherogenic pattern, consisting of an elevated apolipoprotein B-100 (apo B) level, increased number of smaller LDL particles, a reduction in larger HDL particles, and reduced CEC after adjusting for known risk factors for CVD.

Results

Subjects were 13.0 +/- 4.3 years of age (mean +/- standard deviation, unless otherwise noted), with near equal percentage of the two sexes (additional demographics in Table 1). Psoriasis subjects had involvement of 15.7 +/- 3.3 percent body surface area (% BSA; mean +/- standard error), with 25% having mild, 36% moderate, and 39% severe disease based on BSA. Mean duration of psoriasis was 5 +/- 4 years. Body mass index (BMI) was 23.5 +/- 6.1 kg/m2, with 20% being overweight (BMI between 85th and 94th percentile, inclusive) and

27% being obese (BMI 95th percentile). One psoriasis subject had rheumatologist-confirmed psoriatic arthritis, one had polycystic ovarian syndrome, and a third had diagnosed hypertension on drug therapy. None were on lipid-lowering agents. Forty-five percent had a positive family history of psoriasis. Controls had significantly lower BMI values (21.4 +/- 4.3 kg/m2; p=0.03), with 16% being overweight and only 9% obese, along with a lower waist to hip ratio. Smoking and alcohol history were not significantly different between the two groups (one current smoker in each, one case and 3 controls reported occasional alcohol intake). The psoriasis group also had a significantly higher incidence of hypertension, type 2 diabetes, dyslipidemia and coronary artery disease in the family.

Children with psoriasis demonstrated a trend toward higher homeostasis model assessment of insulin resistance (HOMA-IR) values (2.41 vs. 1.99; p=0.11), which was more apparent after log-transformation of HOMA-IR to fit the Gaussian distribution (0.65 vs. 0.41; p=0.07). BMI was the strongest predictor of HOMA-IR (beta 0.49, p <0.001 compared to beta 0.13, p=0.05 for presence of psoriasis and beta 0.29, p<0.01 for waist to hip ratio) in unadjusted regression analyses and on adjustment for age, sex, glucose, systolic blood pressure, and HDL-c. Four of the psoriasis patients had elevated C-reactive protein (CRP) levels, while no controls had abnormal values (p=0.02); these 4 psoriasis subjects were also overweight or obese. Traditional lipid concentrations were not significantly different between children with psoriasis and controls and NMR-measured LDL particle concentration (LDL-p) and size (LDL-z) also did not differ (Table 2). Serum apo B levels, however, were increased in the psoriatic group (72.4 +/- 18.1 vs. 64.6 +/- 16.2; p=0.02). HDL particles tended to be smaller in general (p=0.02), and the number of large HDL particles was decreased in those with skin disease (5.3 +/- 2.9 vs. 6.7 +/- 2.5; p<0.01). The same findings were noted on exclusion of the two psoriasis subjects on systemic therapy and on analysis of plaque type disease alone and guttate and other mixed types alone, compared to their respective controls (data not shown). While increased very low density lipoprotein (VLDL) particle size was mainly noted in overweight and/or obese psoriasis subjects, the trend toward smaller HDL particles and decreased number of large HDL particles became significant only when the normal BMI group was added in addition to the overweight and obese groups. Moreover, apo B levels were elevated even in normal BMI cases compared with their controls (75.4 ± 20.4 vs. 64.2 ±17.5, p=0.02). Psoriasis subjects with a positive family history of type 2 diabetes had increased number of small and total LDL particles relative to those without such family history (p=0.002 and p=0.04, respectively; see Table S2).

A full list of correlations of cholesterol efflux capacity with all cardiometabolic parameters can be found in Supplemental Table 1. As noted in prior studies, HDL-c and apolipoprotein A-1 (apo A-1) levels were strong predictors of efflux capacity (p<0.001 for both), while higher BMI, waist circumference, and HOMA-IR were associated with decreased efflux. In unadjusted analyses, CEC was found to be significantly different between the psoriasis group and controls (0.90 +/-0.15 vs. 0.95 +/- 0.12; p = 0.02), and this decrease in efflux in children with psoriasis remained after adjusting for age, sex, fasting glucose, HOMA-IR, systolic blood pressure, BMI, apo A-1, and HDL-c (beta -0.22, p=0.021; Table 3). These primary estimates did not change when children currently undergoing systemic therapy for psoriasis, including those receiving biologic agents, were excluded. Presence of psoriasis

had greater effect on efflux capacity than having a BMI percentile in the overweight and/or obese range (χ^2= 9.12, p =0.003; Table 4). Those with 5% BSA or greater involvement or Psoriasis Area and Severity Index (PASI) scores 6 or greater showed decreased efflux capacity compared to those with less skin involvement (p=0.02 and p=0.02, respectively; see Figure 1a and 1b). CEC grouped by mild, moderate, and severe skin disease is depicted in Figure S1. Stratified analysis did not demonstrate any ethnic differences in efflux capacity within the psoriasis group (p=0.19), nor any differences based on family history of psoriasis (p=0.10), coronary heart disease (p=0.66), hypertension (p=0.76), or dyslipidemia (p=0.89) (Table S3). However, children with psoriasis and a positive family history of type 2 diabetes mellitus had significantly lower CEC measurements when compared to those with no such family history (0.83 +/- 0.11 vs. 0.96 +/- 0.15, p=0.001; Table S2). Likelihood ratio testing to understand which NMR-estimate HDL parameters best predicted efflux capacity showed that HDL particle size (HDL-z), particle concentration (HDL-p), and cholesterol concentration (HDL-c) were all important factors, but HDL-z had the largest effect of the three (χ^2=19.72, p <0.0001; Table 5).

Discussion

Here we provide, to our knowledge, previously unreported advanced lipoprotein compositional and functional assessments in pediatric psoriasis subjects. Our findings demonstrate an adverse cardiometabolic risk profile even in the early years of skin disease, with a tendency toward increased insulin resistance, a more atherogenic lipoprotein particle profile, and lipoprotein dysfunction as assessed by cholesterol efflux, compared to non-psoriatic controls.

Systemic inflammation has been tied to insulin resistance in murine and human studies, with worsening of both as BMI increases (Esser *et al.*, 2014; Li *et al.*, 2011). Our pediatric psoriasis subjects showed such clustering of inflammation (measured by CRP), overweight and obesity, and greater insulin resistance as estimated by log transformed HOMA-IR. HOMA-IR was used given strong correlation with the gold standard hyperinsulinemic euglycemic clamp technique and easier performance in young children (Henderson *et al.*, 2011). In multivariate regression analyses, BMI was by far the strongest predictor of HOMA-IR, but presence of psoriasis and waist to hip ratio also had some effect. Adult studies have also noted insulin resistance even in non-obese patients with psoriasis (Ucak *et al.*, 2006). Using the euglycemic clamp technique, Gyldenlove et al. found that in normal glucose-tolerant adults, moderate to severe psoriasis subjects demonstrated greater insulin resistance than healthy controls of comparable BMI and body composition (Gyldenlove *et al.*, 2015).

Decreasing calculated or measured LDL cholesterol concentration has for many years been the major goal of lipid-modulating therapies, yet a significant number of CVD-related events occur despite having traditional LDL-c at optimal levels (Cromwell *et al.*, 2007). Studies have shown direct quantification of lipoprotein particles to be more sensitive than LDL-c in identifying future cardiometabolic risk, particularly in chronic conditions with low-grade inflammation such as metabolic syndrome and type 2 diabetes mellitus (Cromwell and Otvos, 2006; Otvos *et al.*, 2011; Rosenson *et al.*, 2010). Consistent with this observation, we

found no difference in LDL-c estimates in our pediatric psoriasis cohort but observed an elevation in a more sensitive metric, apo-B levels. The apo-B concentration corresponds to the total number of atherogenic lipoprotein particles, including VLDL, intermediate density lipoprotein (IDL), and LDL. On the other hand, no significant differences were found in either LDL particle concentration or size in our subjects relative to controls. This is in contrast to our adult psoriasis study, where these parameters were negatively altered, despite more psoriasis patients being on lipid-lowering therapy (Mehta *et al.*, 2012). LDL particle measurements are influenced by traditional CVD risk factors, such as hypertension, dyslipidemia (as measured by traditional lipids), and tobacco use, which were present in the adult psoriasis cohort with increased frequency. These disorders, however, were not yet prominent in our much younger population, where there was mainly excess adiposity but minimal overt clinical disease. These findings suggest that LDL-p may take longer duration of exposure to cardiometabolic diseases to manifest differentially.

Additional tendency toward an atherogenic profile was noted on examining HDL composition in our pediatric subjects. There was a trend toward smaller HDL particle size, and fewer large, HDL particles, similar to the pattern seen in adult psoriasis (Yu *et al.*, 2012). Such profiles have been noted to correlate with coronary atherosclerosis (Arsenault *et al.*, 2009; El Harchaoui *et al.*, 2009). Lower lecithin-cholesterol acyltransferase (LCAT) activity may contribute to the smaller HDL particle size and distribution measured. LCAT is a key enzyme in HDL metabolism and mediates cholesterol esterification, resulting in their partitioning into the core of the HDL particle which increases particle size. Effective therapy for psoriasis has been demonstrated to increase LCAT activity (Holzer *et al.*, 2014). Moreover, vascular inflammation in adult psoriasis has been observed to be associated with these HDL particle changes, as assessed by measuring macrophage activity in atherosclerotic plaques of large vessels using [18F]-fluoro-deoxyglucose-positron emission tomography (Yu *et al.*, 2012). Our study findings suggest that HDL particle size may capture early cardiometabolic effects with greater sensitivity than traditional lipid metrics.

Although traditional HDL cholesterol levels are inversely correlated with CVD events, therapies increasing HDL-c have not shown substantial effect in decreasing their risk, sparking the concept that HDL function is more important to disease outcome than the quantity of HDL (Barter *et al.*, 2007; Khera *et al.*, 2013; Rohatgi *et al.*, 2014). An important anti-atherogenic function of HDL is "reverse cholesterol transport," whereby HDL particles accept cholesterol from lipid-laden macrophages, such as those within atherosclerotic plaques, for transport and eventual biliary excretion. *Ex vivo* measurement of cholesterol efflux capacity using apoB-depleted serum from subjects assesses this property and has been demonstrated in two distinct cohorts to be more influential than HDL-c or apo A-1 levels in predicting atherosclerotic burden and the incidence of CVD events (Khera *et al.*, 2011; Khera and Rader, 2013; Rohatgi *et al.*, 2014). Efflux from macrophages and other aspects of HDL function, such as the anti-oxidative activity of HDL-associated paraoxonase protein, have been shown to be impaired in adults with psoriasis, with improvement in function with effective topical or systemic psoriasis therapy (Holzer *et al.*, 2014; Marsche *et al.*, 2014; Mehta *et al.*, 2012). In our study, children with psoriasis had significantly decreased CEC relative to healthy matched controls before and after adjusting for confounding variables,

suggesting that reverse cholesterol transport defects start early in life even with very low levels of chronic inflammation. Psoriatic disease had greater impact on HDL function than did elevated BMI levels. This provides further evidence of independent negative effects of psoriasis on lipoprotein function and associated unfavorable cardiometabolic risk. More severe skin disease also correlated with greater impairment of CEC, which is in line with other studies that have shown increased metabolic abnormalities with greater psoriasis severity scores (Armstrong *et al.*, 2013; Langan *et al.*, 2012).

In our study, children with psoriasis and normal BMI appeared to have an atherogenic profile even if on a lesser scale, including having elevated apo B levels compared to their normal BMI controls and a trend toward decreased large HDL particle number and HDL size. In addition, our data suggested that aberrations may not be unique to only plaque psoriasis, which is an important finding.

Use of NMR spectroscopy provides reliable and more detailed lipoprotein phenotyping beyond traditional lipid concentration. A main goal of our study was to understand how these more sensitive parameters may detect abnormalities earlier in the pediatric population. In fact, the characterization of lipoprotein particle composition demonstrated that HDL features were different between psoriasis and healthy controls even at this young age. Our study also demonstrated that CEC may be best predicted by HDL particle size, and given the labor involved in assays of cholesterol efflux, NMR spectroscopy may in fact identify multiple features of lipoprotein dysfunction. The use of particle number and size may therefore augment our detection of aberrations in this population at high risk for dyslipidemia in later life.

Overall, our findings support the concept that psoriasis, a condition characterized by a low-level systemic inflammatory state, predisposes to a more atherogenic profile early in the course of disease, and that outcomes which have been well studied in adults, such as obesity, diabetes, and atherosclerotic disease, may start early with precursor changes. This highlights the need to educate physicians (primary care and dermatologists), patients, and families alike regarding these co-morbid conditions and potential future risks and to periodically assess young psoriasis patients for cardiometabolic risk. While screening guidelines have existed for adult psoriasis patients for several years, comparable recommendations are only now in development for children.

Our study was limited by a relatively small sample size; however, this is the largest undertaking in pediatric psoriasis lipoprotein characterization to date. Furthermore, since this was a cross-sectional study, a cause and effect relationship between psoriasis and measured aberrations cannot be proven. A positive family history of type 2 diabetes showed correlation with lipoprotein abnormalities noted in psoriatic subjects, including increased number of small LDL particles, fewer large HDL particles, and decreased cholesterol efflux capacity, and it may therefore itself contribute to risk, or it may serve as a marker for other factors at play (e.g. polymorphic variants of the apo genes). Other potential confounders to address with additional research include ethnic background, effects of previous treatments, and more detailed lifestyle habits including activity and diet. Ongoing prospective studies will better inform a potential temporal relationship.

In conclusion, we demonstrate that there is systemic inflammation, obesity, and a pattern toward insulin resistance, lipoprotein composition abnormalities, and lipoprotein functional modulation in pediatric psoriasis. Studying a larger cohort of children with assessment of cholesterol transport pathways can give insight to underlying pathogenesis, while comparison with affected adults can delineate the impact of disease duration. Further understanding the mechanisms linking these co-morbidities to skin disease (e.g. shared signaling pathways, shared proinflammatory cytokines and adipokines), stratifying patients by risk, and early counseling on lifestyle and other modifications can aid in mitigation of their effects. Future studies should also evaluate whether more vigilant psoriasis therapy will lead to improved cardiometabolic health.

Materials and Methods

The study complied with the Declaration of Helsinki protocols and was approved by the University of California, San Diego Institutional Review Board. Written informed consent was obtained from all subjects. Forty-four children and adolescents, age 0 to 18 years, with active psoriasis and 44 age- and sex-matched healthy controls were enrolled at a dermatology clinic. All races, ethnicities, and psoriasis types (with or without psoriatic arthritis) were allowed, with diagnosis clinically confirmed as typical psoriasis by a dermatologist or pediatric dermatologist. Subjects could not have a diagnosis of congenital heart disease; any prior cardiac catheterizations or surgeries; have taken any cardiac medications (calcium channel blockers, beta blockers, vasotropic medicines) within the past 2 years, other than for hypertension; have other systemic inflammatory disease (including active atopic dermatitis, severe acne, inflammatory bowel disease, juvenile idiopathic arthritis, and connective tissue/autoimmune disease); or have active infection or malignancy. In addition, control subjects could not have a personal or first-degree family history of psoriasis, and they usually presented for evaluation of nevi, birthmarks, warts, or molluscum. Subjects in both groups were consecutively recruited in order to minimize ascertainment bias.

Psoriasis subjects were examined and the % BSA involvement and Psoriasis Area and Severity Index (PASI) score determined. Anthropometric, BMI, and blood pressure measurements were obtained on all subjects and venous blood samples collected after at least 10 hours of fasting. We utilized auto-analyzers to measure serum insulin, glucose, and traditional lipid concentrations, and automated turbidimetric immunoassays for apolipoprotein A-1 and B concentrations (Mayo Medical Laboratories, Rochester, MN). LDL cholesterol concentration (LDL-c) was generated using the Friedwald formula. The homeostasis model assessment of insulin resistance (HOMA-IR) index was used to estimate the degree of insulin resistance [HOMA-IR = fasting glucose (mg/dl) * fasting insulin (mU/ml) / 405]. C-reactive protein was measured as a marker of systemic inflammation.

Ethylenediaminetetraacetic acid was used as the anticoagulant. Lipoprotein particle concentration and diameters were measured using automated NMR spectroscopy (LipoScience Inc., Raleigh, NC). Cholesterol efflux capacity (CEC) was determined as per previously published methods (Khera *et al.*, 2011; Mehta *et al.*, 2012), with slight modifications. J774 cells derived from a murine macrophage cell line were plated and

radiolabeled with 2 microcuries (μCi) of ^{3}H-cholesterol/mL. ATP-binding cassette transporter A1 (ABCA1) was up-regulated by means of a 6-hour incubation with 0.3 mmol/L 8-(4-chlorophenylthio)-cAMP. Subsequently, efflux mediums containing 2.8% apo B-depleted serum from study subjects (prepared as per Mehta *et al.*, 2012) were added for 4 hours. The efflux of radioactive cholesterol from the cells was quantified using liquid scintillation counting. Efflux was calculated by using the following formula: [(μCi of ^{3}H-cholesterol in media containing 2.8% apoB-depleted subject serum – μCi of ^{3}H-cholesterol in serum-free media) ÷ (μCi of ^{3}H-cholesterol in media containing 2.8% apoB-depleted pooled control serum – μCi of ^{3}H-cholesterol in serum-free media). The pooled serum was obtained from five healthy volunteers and run on each plate in duplicates. All assays were performed in duplicate and the mean coefficient of variation of this assay in psoriasis subjects was 4.3% and in controls 3.3%.

Normality was assessed by skewness and kurtosis. Normally distributed continuous variables were compared using student's t-test, while those lacking a normal distribution were compared using the Mann–Whitney U test. Dichotomous variable comparisons were performed using the chi square test. Relationships between variables were determined using Spearman correlation analysis and are reported as Spearman ρ (r) values. Multivariate linear regression analysis was performed using cholesterol efflux capacity (CEC) as the dependent variable and CVD risk factors (age, sex, fasting glucose, HOMA-IR, systolic blood pressure (BP), BMI, apo A-1) and psoriasis evident by skin lesions as independent variables. Sex and psoriasis were adjusted as dichotomous variables in the models; all other variables were continuous. Similar findings were revealed in independent analyses designating sex and psoriasis as dichotomous variables and age, BMI, fasting glucose, HOMA-IR, systolic BP, CEC as continuous variables. Because the magnitude of the estimates of CEC did not differ when fixed- and random-effects regression analyses were performed, we report β-coefficients (β) and p-values for the fixed effects models after adjustment for CVD risk factors.

The relative value of the presence of psoriasis compared to elevated BMI in predicting CEC was determined with likelihood ratio testing applied to nested multivariate regression models.

Finally, because NMR spectroscopy may be more readily available than cholesterol efflux assays and to understand the factor with the strongest contribution to efflux levels, we assessed which NMR-estimate parameters best predicted CEC. Likelihood-ratio testing was performed in nested Tobit models to determine the incremental value of psoriasis as well as HDL-particle size (HDL-z), particle concentration (HDL-p), and cholesterol concentration (HDL-c) in estimation of CEC above and beyond traditional CVD risk factors. The threshold of statistical significance was p 0.05, and all analyses were performed using STATA 12 (College Station, TX).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

References

Armstrong EJ, Harskamp CT, Armstrong AW. Psoriasis and major adverse cardiovascular events: a systematic review and meta-analysis of observational studies. J Am Heart Assoc. 2013; 2:e000062. [PubMed: 23557749]

Arsenault BJ, Lemieux I, Despres JP, et al. HDL particle size and the risk of coronary heart disease in apparently healthy men and women: the EPIC-Norfolk prospective population study. Atherosclerosis. 2009; 206:276–81. [PubMed: 19268944]

Augustin M, Glaeske G, Radtke MA, et al. Epidemiology and comorbidity of psoriasis in children. Br J Dermatol. 2010; 162:633–6. [PubMed: 19922529]

Barter PJ, Caulfield M, Eriksson M, et al. Effects of torcetrapib in patients at high risk for coronary events. N Engl J Med. 2007; 357:2109–22. [PubMed: 17984165]

Cromwell WC, Otvos JD. Heterogeneity of low-density lipoprotein particle number in patients with type 2 diabetes mellitus and low-density lipoprotein cholesterol <100 mg/dl. Am J Cardiol. 2006; 98:1599–602. [PubMed: 17145217]

Cromwell WC, Otvos JD, Keyes MJ, et al. LDL Particle Number and Risk of Future Cardiovascular Disease in the Framingham Offspring Study - Implications for LDL Management. J Clin Lipidol. 2007; 1:583–92. [PubMed: 19657464]

El Harchaoui K, Arsenault BJ, Franssen R, et al. High-density lipoprotein particle size and concentration and coronary risk. Ann Intern Med. 2009; 150:84–93. [PubMed: 19153411]

Esser N, Legrand-Poels S, Piette J, et al. Inflammation as a link between obesity, metabolic syndrome and type 2 diabetes. Diabetes Res Clin Pract. 2014; 105:141–50. [PubMed: 24798950]

Ferretti G, Simonetti O, Offidani AM, et al. Changes of plasma lipids and erythrocyte membrane fluidity in psoriatic children. Pediatr Res. 1993; 33:506–9. [PubMed: 8511025]

Gyldenløve M, Storgaard H, Holst JJ, et al. Patients with psoriasis are insulin resistant. J Am Acad Dermatol. 2015; 72:599–605. [PubMed: 25653028]

Henderson M, Rabasa-Lhoret R, Bastard JP, et al. Measuring insulin sensitivity in youth: How do the different indices compare with the gold-standard method? Diabetes Metab. 2011; 37:72–8. [PubMed: 21126900]

Holzer M, Wolf P, Curcic S, et al. Psoriasis alters HDL composition and cholesterol efflux capacity. J Lipid Res. 2012; 53:1618–24. [PubMed: 22649206]

Holzer M, Wolf P, Inzinger M, et al. Anti-psoriatic therapy recovers high-density lipoprotein composition and function. J Invest Dermatol. 2014; 134:635–42. [PubMed: 23985995]

Khera AV, Cuchel M, de la Llera-Moya M, et al. Cholesterol efflux capacity, high-density lipoprotein function, and atherosclerosis. N Engl J Med. 2011; 364:127–35. [PubMed: 21226578]

Khera AV, Patel PJ, Reilly MP, et al. The addition of niacin to statin therapy improves high-density lipoprotein cholesterol levels but not metrics of functionality. J Am Coll Cardiol. 2013; 62:1909–10. [PubMed: 23933538]

Khera AV, Rader DJ. Cholesterol efflux capacity: full steam ahead or a bump in the road? Arterioscler Thromb Vasc Biol. 2013; 33:1449–51. [PubMed: 23766382]

Koebnick C, Black MH, Smith N, et al. The association of psoriasis and elevated blood lipids in overweight and obese children. J Pediatr. 2011; 159:577–83. [PubMed: 21524758]

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; 132:556–62. [PubMed: 22113483]

Li RC, Krishnamoorthy P, DerOhannessian S, et al. Psoriasis is associated with decreased plasma adiponectin levels independently of cardiometabolic risk factors. Clin Exp Dermatol. 2014; 39:19–24. [PubMed: 24341476]

Li ZY, Wang P, Miao CY. Adipokines in inflammation, insulin resistance and cardiovascular disease. Clin Exp Pharmacol Physiol. 2011; 38:888–96. [PubMed: 21910745]

Marsche G, Holzer M, Wolf P. Antipsoriatic treatment extends beyond the skin: recovering of high-density lipoprotein function. Exp Dermatol. 2014; 23:701–4. [PubMed: 24980461]

Mehta NN, Li R, Krishnamoorthy P, et al. Abnormal lipoprotein particles and cholesterol efflux capacity in patients with psoriasis. Atherosclerosis. 2012; 224:218–21. [PubMed: 22858285]

Mehta NN, Yu Y, Saboury B, 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; 147:1031–9. [PubMed: 21576552]

Otvos JD, Jeyarajah EJ, Bennett DW, et al. Development of a proton nuclear magnetic resonance spectroscopic method for determining plasma lipoprotein concentrations and subspecies distributions from a single, rapid measurement. Clin Chem. 1992; 38:1632–8. [PubMed: 1326420]

Otvos JD, Mora S, Shalaurova I, et al. Clinical implications of discordance between low-density lipoprotein cholesterol and particle number. J Clin Lipidol. 2011; 5:105–13. [PubMed: 21392724]

Paller AS, Mercy K, Kwasny MJ, et al. Association of pediatric psoriasis severity with excess and central adiposity: an international cross-sectional study. JAMA Dermatol. 2013; 149:166–76. [PubMed: 23560297]

Rajappa M, Rathika S, Munisamy M, et al. Effect of treatment with methotrexate and coal tar on adipokine levels and indices of insulin resistance and sensitivity in patients with psoriasis vulgaris. J Eur Acad Dermatol Venereol. 2015; 29:69–76. [PubMed: 24665910]

Rizzo JA, Mallow PJ, Waters HC, et al. Managing to low-density lipoprotein particles compared with low-density lipoprotein cholesterol: a cost-effectiveness analysis. J Clin Lipidol. 2013; 7:642–52. [PubMed: 24314363]

Rohatgi A, Khera A, Berry JD, et al. HDL cholesterol efflux capacity and incident cardiovascular events. N Engl J Med. 2014; 371:2383–93. [PubMed: 25404125]

Rosenson RS, Davidson MH, Pourfarzib R. Underappreciated opportunities for low-density lipoprotein management in patients with cardiometabolic residual risk. Atherosclerosis. 2010; 213:1–7. [PubMed: 20451205]

Samarasekera EJ, Neilson JM, Warren RB, et al. Incidence of cardiovascular disease in individuals with psoriasis: a systematic review and meta-analysis. J Invest Dermatol. 2013; 133:2340–6. [PubMed: 23528816]

Torres T, Machado S, Mendonca D, et al. Cardiovascular comorbidities in childhood psoriasis. Eur J Dermatol. 2014; 24:229–35. [PubMed: 24752043]

Ucak S, Ekmekci TR, Basat O, et al. Comparison of various insulin sensitivity indices in psoriatic patients and their relationship with type of psoriasis. J Eur Acad Dermatol Venereol. 2006; 20:517–22. [PubMed: 16684277]

Yu Y, Sheth N, Krishnamoorthy P, et al. Aortic vascular inflammation in psoriasis is associated with HDL particle size and concentration: a pilot study. Am J Cardiovasc Dis. 2012; 2:285–92. [PubMed: 23173102]

Abbreviations

CVD	cardiovascular disease
LDL	low density lipoprotein
HDL	high density lipoprotein
apo A-1	apolipoprotein A-1

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apo B   apolipoprotein B-100

CEC   cholesterol efflux capacity

HOMA-IR   homeostasis model assessment of insulin resistance
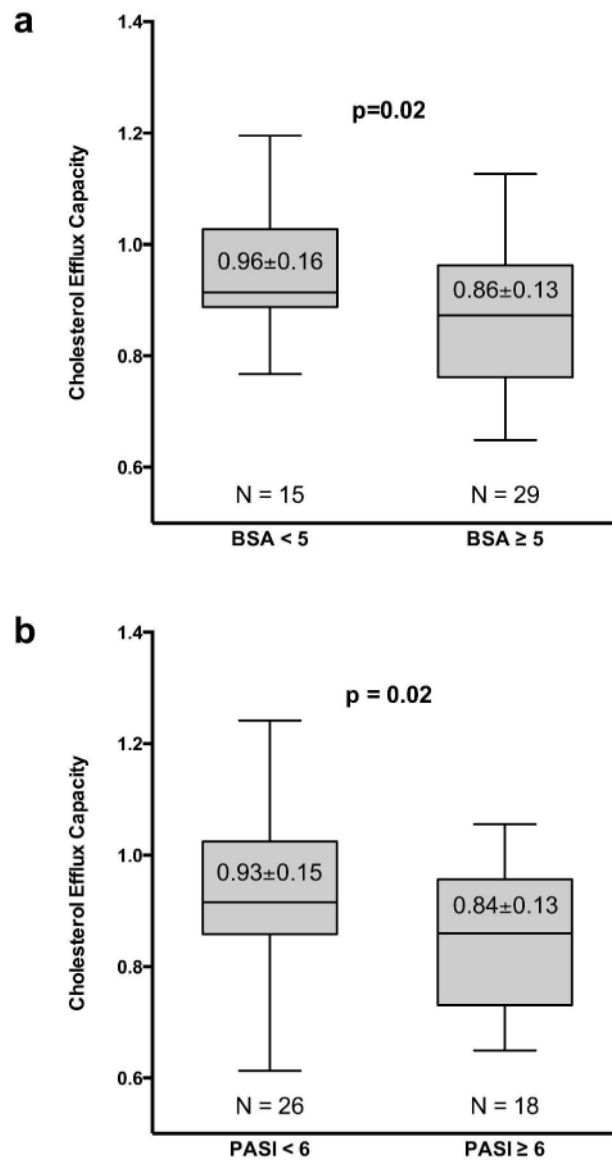
Figure 1.
Cholesterol efflux capacity by psoriasis disease severity.

a. depicts efflux capacity by psoriasis severity as measured by percent body surface area (% BSA), with 15 subjects with <5% BSA affected and 29 with 5% BSA affected.

b. depicts efflux with psoriasis severity measured by the Psoriasis Area and Severity Index (PASI), with 26 subjects with PASI <6 and 18 with PASI 6.

Efflux capacity is expressed as a proportion normalized to a known pooled serum sample from five healthy volunteers (Mean ± SD given; p-value derived from T-test with equal variance)

Table 1

General characteristics of the study groups

Parameter[1]	Psoriasis (n=44)	Controls (n=44)	p-value*
Age (years)	13.0 ± 4.3	13.0 ± 4.3	Matched
Male	19 (43%)	19 (43%)	Matched
Race/Ethnicity:			
Caucasian	19 (43%)	20 (45%)	0.35
African American	2 (5%)	6 (14%)	
Hispanic	19 (43%)	13 (30%)	
Other	4 (9%)	5 (11%)	
Family history:			
Diabetes	23 (52%)	11 (26%)	**0.01**
Hypertension	26 (59%)	9 (22%)	**0.001**
Dyslipidemia	15 (34%)	5 (12%)	**0.01**
Coronary Artery Disease/Myocardial Infarction	18 (41%)	5 (12%)	**0.002**
Anthropometric and Blood pressure measures:			
BMI (kg/m^2)	23.5 ± 6.1	21.4 ± 4	**0.03**
BMI percentile	72 ± 28	67 ± 25	0.8
Waist circumference (cm)	80.5 ± 17.9	74.3 ± 12.5	**0.04**
Waist-to-hip ratio	0.85 ± 0.06	0.80 ± 0.06	**<0.001**
Systolic BP (mm Hg)	116 ± 11	116 ± 15	0.57
Diastolic BP (mm Hg)	63 ± 9	66 ± 9	0.1
Systolic BP percentile	68 ± 27	66 ± 29	0.64
Diastolic BP percentile	47 ± 26	54 ± 24	0.1
Psoriasis type:			
Plaque	26 (59%)		
Guttate	5 (11%)		
Mixed lesion types	13 (30%)		
Number with concomitant psoriatic arthritis Psoriasis severity:	1 (2%)		
Percent Body Surface Area (% BSA), Mean (SEM)	15.7 (3.3)		
- Mild disease (<3% BSA)	11 (25%)		
- Moderate disease (3-10% BSA)	16 (36%)		
- Severe disease (>10% BSA)	17 (39%)		
Psoriasis Area and Severity Index (PASI)	5.7 ± 5.2		
Current treatment:			
Topical therapy alone	38 (86%)		
Phototherapy	0 (0%)		
Systemic therapy	2 (5%)		
Not on therapy	4 (9%)		

Abbreviations: BMI, body mass index; BP, blood pressure

[1]Note: All continuous variables expressed as Mean±SD and categorical variables as N (%) unless otherwise specified

*Simple t-test or Mann Whitney U test for continuous variables and Pearson's chi-square test for categorical variables; p 0.05 considered significant

Table 2

Lab parameters and NMR spectroscopy profile of the study groups

Parameter[2]	Psoriasis (n=44)	Controls (n=44)	p-value[#]
Labs:			
CRP (mg/L)	0.24 ± 0.71	0.02 ± 0.11	**0.02**
Homocystine (μmol/L)	7.0 ± 1.9	7.4 ± 2.5	0.77
Metabolic assessment:			
Insulin (mU/ml)	11.8 ± 8.9	9.8 ± 6.6	0.11
Glucose (mg/dl)	79.5 ± 7.8	80.1 ± 8.1	0.63
HOMA-IR	2.41 ± 1.83	1.99 ± 1.38	0.11
log Transformed HOMA-IR	0.65 ± 0.68	0.41 ± 0.88	0.07
Lipid profile: (mg/dl)			
Total cholesterol	168.8 ± 34.3	161.1 ± 29.9	0.13
LDL-c	102.3 ± 29.6	93.8 ± 24.6	0.33
HDL-c	49.5 ± 13.4	50.4 ± 10.3	0.65
Triglycerides	88.4 ± 32.7	84.9 ± 38.6	0.33
Cholesterol: HDL-c ratio	3.6 ± 1.0	3.3 ± 0.8	0.25
Apolipoprotein A	140.3 ± 24.7	135.2 ± 17.6	0.13
Apolipoprotein B	72.4 ± 18.1	64.6 ± 16.2	**0.02**
NMR spectroscopy:			
<u>VLDL Particle (VLDL-p) concn., nmol/L</u>			
Total VLDL-p	44.4 ± 13.8	45.6 ± 21.8	0.38
Small VLDL-p	31.2 ± 10.4	33.3 ± 15.7	0.76
Medium VLDL-p	11.5 ± 6.3	10.7 ± 7.6	0.29
Large VLDL-p	2.4 ± 1.4	2.4 ± 2.3	0.45
<u>LDL Particle (LDL-p) concn., nmol/L</u>			
Total LDL-p	690.3 ± 287.5	662.1 ± 244.2	0.69
Small LDL-p	228.5 ± 162	239 ± 136.2	0.63
Large LDL-p	153.9 ± 120	136.5 ± 110.5	0.75
<u>HDL Particle (HDL-p) concn., μmol/L</u>			
Total HDL-p	30.6 ± 4.5	31.1 ± 4.8	0.71
Small HDL-p	13.4 ± 5.2	12.3 ± 4.3	0.13
Medium HDL-p	10.5 ± 4.4	10.6 ± 6.2	0.52
Large HDL-p	5.3 ± 2.9	6.7 ± 2.5	**<0.01**
<u>Mean Particle Size (-z), nm</u>			
VLDL-z	47.0 ± 4.2	46.9 ± 5.4	0.45
LDL-z	20.7 ± 0.5	20.7 ± 0.6	0.55
HDL-z	9.4 ± 0.5	9.6 ± 0.4	**0.02**
Cholesterol efflux capacity:	0.90 ± 0.15	0.95 ± 0.12	**0.02**

NMR= Nuclear Magnetic Resonance; CRP= C-reactive protein; TNF=Tumor Necrosis Factor; HOMA-IR=Homeostasis Assessment of Insulin Resistance; LDL= Low-density lipoprotein; HDL= High-density lipoprotein; VLDL=Very low-density lipoprotein; IDL= Intermediate density lipoprotein; concn=concentration.

[2]Note: All continuous variables expressed as Mean±SD

[#]p-value derived from simple t-test or Mann Whitney U tests; p 0.05 considered significant

Table 3

Regression analysis of the association of psoriasis with cholesterol efflux capacity, with adjustment for cardiometabolic variables

Covariates	Beta	p-value
Model[a]	−0.29	**0.004**
Model[a] + **HDL-c**	−0.22	**0.021**
Model[a] + **HDL-z**	−0.19	**0.047**
Model[a] + **HDL-p**	−0.25	**0.013**

Model[a] - Adjusted for age, sex, fasting glucose, HOMA-IR, Systolic BP, BMI & apolipoprotein A.

Note: Beta=Standardized regression coefficient; p 0.05 considered significant

Table 4

Relative value of the presence of psoriasis and elevated body mass index in predicting cholesterol efflux capacity

Nested models[*]	χ2	p-value
Psoriasis added to model[b]	9.12	**0.003**
Obesity added to model[b]	0.45	0.5
Overweight-obese added to model[b]	0.49	0.48
Psoriasis added to obesity in model[b]	8.68	**0.003**
Obesity added to Psoriasis in model[b]	0.02	0.89
Psoriasis added to overweight-obese in model[b]	8.63	**0.003**
Overweight-obese added to Psoriasis in model[b]	0.01	0.94

Model[b] - Age, sex, fasting glucose, HOMA-IR, Systolic BP, LDL, & apolipoprotein A;

[*] Likelihood ratio testing was applied to nested multivariate regression models to assess the incremental value of psoriasis and obesity in predicting cholesterol efflux capacity; p 0.05 considered significant.

Obesity defined as body mass index (BMI) 95th percentile, Overweight-obese defined as BMI 85th percentile

Table 5

Relative value of HDL-particle size, HDL-particle number and HDL cholesterol concentration in predicting cholesterol efflux capacity

Nested models[*]	$\chi 2$	p-value
HDL-p added to model[a]	6.43	**0.01**
HDL-c added to model[a]	37.19	**<0.0001**
HDL-z added to model[a]	19.72	**<0.0001**
HDL-c added to HDL-z in model[a]	2.42	0.12
HDL-z added to HDL-c in model[a]	19.89	**<0.0001**
HDL-p added to HDL-z in model[a]	16.46	**0.0001**
HDL-z added to HDL-p in model[a]	29.76	**<0.0001**
HDL-p added to HDL-c in model[a]	0.31	0.58
HDL-c added to HDL-p in model[a]	31.08	**<0.0001**

Model[a] - Age, sex, fasting glucose, HOMA-IR, Systolic BP, BMI & apolipoprotein A.

[*] Likelihood ratio testing was applied to nested multivariate regression models to assess the incremental value of HDL-z, HDL-p and HDL-c in predicting cholesterol efflux capacity; p 0.05 considered significant.