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Association Between Oxidation-Modified Lipoproteins and Coronary Plaque in Psoriasis: An Observational Cohort Study

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Abstract

Rationale: Psoriasis (PSO) is a systemic inflammatory skin disease associated with cardiovascular disease (CVD) and lipid dysfunction. However, traditional lipid parameters have limited prognostic value whereas assessing oxidation-modified lipids (OMLs) in this inflammatory driven condition may capture additional risk. Recently, a study showed that PSO was associated with increased lipid rich coronary plaques, therefore, investigating potential relationships with OMLs may speed understanding of increased CVD in PSO.

Objective: To understand whether OMLs associate with traditional lipid phenotypes, cardiometabolic disease biomarkers and total coronary plaque, with focus on non-calcified burden (NCB) by CCTA in psoriasis.

Methods and Results: PSO subjects and controls (n=252) had profiling for oxidation-modified LDL, HDL, Lp(a), cholesterol efflux capacity (CEC), lipoprotein particle size and number by NMR spectroscopy and paraoxonase (PON1) activity. Blinded CCTA coronary artery disease

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characterization included total burden (TB), NCB and dense-calcified burden (DCB). Compared to healthy volunteers (HV), PSO subjects were older (mean age=50.1), had increased BMI and HOMA-IR. PSO subjects had increase in oxLp(a), Lp(a) and oxHDL ($p<0.05$ for all) with significant association of oxLDL ($\beta=0.10$, $p=0.020$) and oxHDL ($\beta=-0.11$, $p=0.007$) with NCB. Moreover, PSO subjects expressed significantly higher PON1 (kU/ μ l) activity compared to HV (8.55 ± 3.21 vs. 6.24 ± 3.82 , $p=0.01$). Finally, PSO treatment was associated with a reduction in oxHDL (U/ml) (203.79 ± 88.40 vs. 116.36 ± 85.03 , $p<0.001$) and with a concomitant decrease in NCB at one year (1.04 ± 0.44 vs. 0.95 ± 0.32 , $p=0.03$).

Conclusions: Traditional lipids did not capture risk of lipid rich plaque as assessed by NCB, whereas assaying oxidation-modification of lipids revealed significant association with oxLDL and oxHDL. The PON-1 activity was increased in PSO suggesting possible compensatory anti-oxidative effect. Psoriasis treatment was associated with a reduction in oxHDL. These findings support performance of larger studies to understand oxidation-modified lipids in inflammatory states.

Keywords

Psoriasis; inflammation; atherosclerosis; oxidized lipids; coronary CT angiography; Cardiovascular Disease; Coronary Artery Disease; Lipids and Cholesterol

INTRODUCTION

Psoriasis (PSO) is a chronic systemic inflammatory skin disease associated with dyslipidemia¹, altered HDL composition and impaired cholesterol efflux capacity²; all of these factors contributing to accelerated atherosclerotic cardiovascular complications in psoriasis³. Considering that this pathological condition adds a cumulative risk to early cardiovascular disease (CVD) development in a relatively young population, effective prognostic tools are needed to adequately capture and monitor CVD risk. Estimating disease specific lipid modifications may add value for CVD risk assessment.

Oxidized low-density lipoprotein (oxLDL) significantly contributes to atherosclerosis propagation and remains an important target for treatment of CVD^{4,5}. Based on the structural and functional similarities between lipoprotein(a) [Lp(a)] and LDL, the former has gained traction as a more reliable marker for CVD processes related to aging including aortic stenosis⁶. However, lack of commercially available diagnostic tools for estimating oxidized Lp(a) and oxidized high-density lipoprotein (oxHDL) has significantly hindered the availability of data for more intense investigation. Limited studies utilizing highly sensitive liquid chromatography tandem mass spectrometry (LC-MS/MS), oxidized phospholipids (oxPLs) contained within Lp(a) have been shown to augment the pro-inflammatory response and promote CVD progression, an effect that was attenuated with inactivation of oxPLs⁷. Additionally, lower oxHDL also had pro-atherosclerotic effects and was accompanied by significant immunological responses⁸.

On the contrary, emerging data suggest that low concentrations of oxPLs transported by oxLDL, oxLp(a) and oxHDL can confer more homeostatic than pro-inflammatory effects. Downstream signaling of PLs and its oxidized counterparts involve completely separate

pathways and are dependent on their overall as well as relative concentrations within the circulation secondary to the disease state ⁹. Moreover, it has been shown that psoriasis patients have decreased cholesterol-efflux capacity (CEC) ², which in a single small study showed changes in phospholipid content of HDL composition after PSO treatment. Additionally, biologically active oxidized lipid mediators (LMs) derived from arachidonic and linoleic acids are esterified in cholesterol ester (CE) and PL transported by oxLDL and oxHDL ^{10, 11}. These lipid mediators are highly abundant in psoriasis skin and play critical role in processes of inflammation initiation and resolution ¹². A recent study showed that lower oxHDL levels were associated with higher CVD risk in young healthy population ¹³. Another contributing factor to the reported HDL abnormalities may in part be due to low anti-oxidative properties as of paraoxonase-1 (PON1) enzyme activity ^{14, 15}. However, most of the studies reported ambiguous data on the PON1 enzyme activity and need further analysis and clarification.

Coronary CT Angiography (CCTA) provides a non-invasive imaging measurement of coronary plaque parameters and its respective subcomponents, including both dense calcified (DCB) and non-calcified plaque burden (NCB) ¹⁶. These CCTA-derived coronary plaque parameters have been utilized as a reliable predictor of future cardiovascular events ¹⁷. Considering that traditional lipid parameters may not be adequately affected by psoriasis disease processes and related treatments ¹⁸, we hypothesized that oxidation-modified lipoproteins might serve as a promising tool for early heart disease detection and evaluation by CCTA. Indeed, the low anti-oxidative state of psoriasis patients and high circulating levels of oxidation-modified lipid mediators ¹², along with an increase in high-risk lipid rich coronary plaque as assessed by NCB ¹⁹, may provide a window to investigate and understand these associations in CVD.

METHODS

The data that support the findings of this study are available to qualified researchers trained in human subject confidentiality protocols from the corresponding author upon reasonable request.

All the enrolled 245 consecutive subjects with psoriasis were part of an ongoing NIH cohort study (Figure 1). A detailed description of methods and materials including inclusion/exclusion criteria, clinical assessment, detailed imaging procedures, and statistical analyses for both the cohorts are available in the online-only supplement. STROBE guidelines were followed for reporting the findings from both the stages ²⁰.

RESULTS

Study population.

Psoriasis (PSO) subjects (n=232) were middle-aged (mean [SD] age, 50.13 [12.64] years), predominantly male (n=136; 58%), and at low cardiovascular risk by Framingham risk score (FRS) (median, 4.02; interquartile range [IQR], 1-6), with a moderate skin disease [PASI score, median (IQR), 7.9 (2.8-10.0)] (Table 1), and high-sensitivity C-reactive protein (hsCRP) higher in PSO cohort (median [IQR], 4.48 [0.80-4.22] vs. 1.24 [0.60-1.00],

P=0.002) compared to healthy volunteers (HV). Almost half of the PSO cohort has been diagnosed with hyperlipidemia (n=105; 45%) and among them 71 (68%) were on lipid-lowering treatment. Established lipid parameters including TG, Lp(a) and ApoB were significantly elevated in PSO patients compared to HV. Moreover, there were higher levels of oxHDL and oxLp(a) in PSO plasma when compared to HV.

Characterization of oxidation-modified lipoproteins in psoriasis.

OxLDL.—Although oxLDL levels at baseline were non-significantly higher in the PSO group (Table 1), they were positively associated with some of the known CVD parameters, including hyperlipidemia, body mass index, and FRS (Table 2). Further analysis of CCTA-derived plaque parameters with traditional lipids (Table 3, 3A) and advance lipid phenotype showed significant positive association between NCB and oxLDL ($\beta=0.10$, $p=0.02$) (Table 3, 3B-D), which remained significant beyond adjustment for traditional cardiovascular risk factors, lipid lowering therapy and systemic or biologic psoriasis therapy ($\beta=0.12$, $p=0.006$) (Table 4). NMR lipid analysis showed predominant contribution of small LDL particles to the observed oxLDL association (Table 3, 3B) whereas ApoB did not show significant contribution (Table 3, 3C). To determine whether skin disease severity affected these relationships, we stratified by disease severity and found disparate findings. Severe patients had a strong negative correlation between oxLDL and DCB, whereas mild psoriasis severity showed even stronger positive correlation with NCB and TB (Table 5).

OxHDL.—oxHDL baseline levels were significantly higher in the PSO group compared to HV (mean [SD], 202.89 ± 175.62 vs. 176.88 ± 216.25 ; $p=0.02$) (Table 1). In contrast to oxLDL, oxHDL had a significant negative association with most of the CVD parameters (Table 2). TB and NCB had significant negative association with HDL-C (Table 3, 3A) and oxHDL ($\beta=-0.12$, $p=0.007$) (Table 3, 3D). Such association remained significant beyond traditional cardiovascular risk factors, lipid lowering therapy and systemic or biologic psoriasis therapy ($\beta=-0.12$, $p=0.006$) (Table 4). NMR lipid analysis showed predominant role of large HDL particles and inverse association with small LDL particles to the observed oxHDL associations (Table 3, 3B) along with significant Apo-A1 contribution. Of note, the same stratification approach of the PSO group for different skin disease severity revealed opposite correlation for NCB and DCB compared to oxLDL (Table 5). More severe (PASI>10) patients had strong positive correlation of oxHDL with DCB, whereas moderate (PASI<10) psoriasis severity showed negative correlation with NCB and TB.

OxLp(a) and Lp(a).—Both lipid parameters were significantly elevated in psoriasis group compared to healthy volunteers at baseline (Table 1). Strong positive association was observed for Lp(a) with age, female sex, hyperlipidemia and glucose (Table 2). However, no significant association was observed for coronary plaque burden parameters, Table 3. Further adjustment for conventional risk factors did not reveal any significant associations either (Table 4). Lp(a) was mainly associated with small vldl particles, whereas oxLp(a) was negatively associated with large ldl particles (Table 3, 3B). Notably, further stratification of psoriasis group for different psoriasis severity showed significant positive correlation of oxLp(a) with TB and NCB in patients with less severe disease and negative for NCB in

patients with severe psoriasis. In contrary, stratification for Lp(a) did not reveal any significant correlation (Table 5).

PON1 activities and its relation to oxidation-modified lipids in psoriasis patients.

The PON1 system determines HDL antioxidative properties in vivo and contributes to the CVD risk²¹. To address the potential variation in the PON1 activities and clarity of measurements, we included additional PSO subjects (Online Table I) from our general cohort with serum samples stored for up to 2 years maximum. This group consisted of 40 middle-aged individuals (mean [SD] age, 50.45 [13.02] years), predominantly male (n=24; 60%) and a PASI score of 7.9 (IQR, 3.4-11.0). Overall, this additional group did not differ significantly from the main cohort. PSO subjects had significantly higher paraoxonase activity compared to HV (8.55 ± 3.21 vs. 6.24 ± 3.82 , $p=0.01$). However, arylesterase activity had a lower trend in PSO compared to HV and lactonase activity did not differ between PSO and HV group (Online Table I).

Association of psoriasis treatment with oxidation-modified lipoproteins.

PSO patients stratified by systemic or biologic agents at baseline showed a positive association between oxLDL and both TB and NCB, and a negative association between oxLDL and DCB (Table 5). Furthermore, per our protocol, moderate-severe psoriasis patients who start a new biologic during the study period (biologic naïve) are seen 3-5 months following therapy. In this group, (Table 6) patients were middle-aged (mean [SD] age, 46.7 [13.29] years), predominantly male (55%), and at low cardiovascular risk by Framingham risk score (median, 2.4; IQR, 1-2), with treatment consisting of anti-TNF (n=8, 40%), anti-IL17 (n=7, 35%) and anti-IL12/23 (n=5, 25%) therapy. At 3-5-month follow-up, we observed a statistically significant increase in TG along with increasing trend in Lp(a) compared to baseline along with a decrease in oxHDL (203.79 ± 88.40 vs. 116.36 ± 85.03 , $p=0.0005$). OxLDL and oxLp(a) showed concomitant non-significant decreasing trend at follow-up. In this group, at one-year, we observed a reduction in total coronary plaque burden (TB) (mean [SD], 1.09 [0.40] vs 1.00 [0.31]; $P=0.01$) primarily driven by a reduction in NCB (mean [SD], 1.04 [0.44] vs 0.95 [0.32]; $P=0.03$) with change in DCB (Table 6).

DISCUSSION

In our study investigating the relationship between oxidation-modified lipids (OMLs) and coronary plaque by CCTA in psoriasis, we demonstrate: (1) psoriasis was associated with increased levels of many OMLs as compared to healthy volunteers; (2) while oxLDL was directly associated with NCB, oxHDL was inversely associated with both total and non-calcified coronary plaque and (3) treatment of psoriasis with anti-inflammatory biologic therapy reduced oxHDL concurrent with a decrease in NCB at one-year. Collectively, these findings suggest that circulating OML levels may be a useful marker of early atherosclerosis by CCTA in psoriasis.

Psoriasis-associated cardiovascular disease.

Psoriasis, a chronic inflammatory skin disease, is associated with heightened risk for MI in young psoriasis patients-translating to roughly five years of life lost^{22, 23}. Moreover,

dyslipidemia is one of the most prevalent comorbidities in psoriatic patients²⁴. Coronary computed tomography angiography is a reliable, non-invasive imaging technique that allows for quantification and characterization of total and non-calcified coronary plaque. Prior work has demonstrated that TB and NCB predict prospective CV events in patients without inflammatory condition^{25, 26}. Psoriasis is associated with higher non-calcified plaque in the coronary arteries, a finding shown to be reduced by anti-inflammatory treatment¹⁹ in a small observational study. Since non-calcified coronary plaque is most often the culprit lesion in MI, we utilized CCTA derived plaque indices to understand the epidemiological association between NCB and oxidized lipids for early characterization of subclinical atherosclerosis.

Significant lipid composition and function disturbances associate with immunologic abnormalities in psoriasis^{2, 27–29}. Most notably, the chronic, systemic inflammation of psoriasis is associated with altered HDL function. Beyond reverse cholesterol transport, HDL with its anti-oxidative, anti-inflammatory, anti-apoptotic and anti-thrombotic functions contribute considerably to mitigate atherosclerosis³⁰. Systemic and vascular inflammation, however, has been proposed to convert HDL to a dysfunctional form and impair these protective properties, in effect promoting CVD³¹. Psoriasis patients have a more atherogenic lipoprotein profile and decreased HDL efflux capacity³². Furthermore, inflammatory mediators, including adipocyte-derived cytokines such as TNF- α , IL-6, and leptin, are known to induce dyslipidemia. These derangements may in part help explain the accumulated evidence of an epidemiological association between psoriasis and CVD. As such, psoriasis provides a useful model to understand the close relationships between lipoprotein dysfunction and early subclinical coronary atherosclerosis assessed by CCTA.

Oxidation-modified lipids in cardiovascular disease.

Psoriasis-related inflammation and oxidative stress are associated with higher lipoprotein oxidation, dyslipidemia, cardiovascular disease progression, even when LDL has been treated to target levels^{33, 34}. Collectively, OMLs are critical to atherosclerosis progression since they are involved in foam cell generation, endothelial and smooth muscle cell dysfunction^{35, 36}, and other inflammatory reactions, including subendothelial activation and vascular inflammation³⁷. Furthermore, circulating OMLs are associated with subclinical atherosclerosis as well as hard cardiovascular events^{38, 39}.

Most phases of atherosclerosis are driven by the inflammatory cascade. It is well known that oxidation of LDL initiates cascade of biochemical reactions leading to endothelial cell dysfunction and atherosclerotic plaque formation⁴ – explaining the association between early plaque and ox-LDL. In-vitro experiments have shown low doses of oxLDL to be sufficient enough to activate macrophages and mast cells and synergistically increase monocyte-endothelium adhesion, while higher doses of oxLDL had less profound effect⁴⁰. Thus, the reported immunological activation by oxLDL contributes to endothelial dysfunction and early atherogenesis, dependent on the chronicity/severity of the underlying inflammatory milieu.

Oxidation-modified lipids and non-calcified coronary plaque in psoriasis.

In our study, psoriasis patients had significantly higher levels of oxHDL, and oxLp(a) compared to healthy volunteers. oxLDL also trended but was not statistically significant. Moreover, we demonstrated a bidirectional association between each oxidation-modified lipoprotein class and NCB, when stratified by psoriasis disease severity¹¹. Furthermore, oxLDL showed strong positive correlation with NCB and TB even after adjusting for multiple cardiovascular risk factors. Oxidative modification of LDL is one of the earliest events in the pathogenesis of atherosclerosis, subsequently promoting an inflammatory environment and lipid deposition in the arterial wall. We confirm this association in a cohort of psoriasis patients, similar to the previously reported associations in general population. While Lp(a) is considered to be a more sensitive alternative to LDL in estimating cardiovascular risk and has been shown to mediate MI, stroke, and peripheral arterial disease⁶, its role in chronic inflammatory disease states needs further exploration. Though we present an association between oxLp(a) and NCB, further mechanistic studies need to elucidate the impact of oxidation of Lp(a) and subsequently its role in propagating the lipid-rich non-calcified plaque.

While research on OMLs has primarily focused on LDL, other plasma lipoproteins are also susceptible to oxidative modification. In recent years, oxHDL has gained interest in pathogenesis of atherosclerosis, especially with advancement in our understanding of the various pathways that lead to HDL oxidation and affect its role of reverse cholesterol transport. oxHDL contribution to atherosclerosis has been postulated to be in an opposite way as oxLDL¹³, possibly due to the HDL proteome shifting to a proinflammatory, oxidative phenotype during psoriasis progression. This may be mediated through oxidative and immune-driven derangements of ApoA1, resulting in reduced HDL efflux and complete or partial loss of HDL's anti-inflammatory functions. Taken together, this is consistent with our finding that severe psoriasis patients had strong positive correlation of oxHDL with DCB, while mild-moderate severity showed negative correlation with NCB and TB.

Another possible explanation of the observed findings might be related to differing concentrations of bioactive lipid mediators within local tissues and the systemic circulation. PSO skin and peripheral blood represent a diverse source of bioactive lipid mediators, which have potent effects on inflammation progression and resolution. Specifically, PSO lesional skin is abundant in oxidized LMs⁴¹ derived from arachidonic and linoleic acids which predominantly have dietary source. Importantly, the main cargo of these oxidized LMs in circulation is LDL. The excess amount of these LMs in PSO inflamed skin require high concentrations of LDL and a compensatory increase in HDL. These could be susceptible to increased oxidation in PSO disease partly explained by linoleic acid-derived oxidized bioactive lipid mediators which are also highly present on the oxHDL and explicit protective function¹¹. Furthermore, oxidation products of these polyunsaturated fatty acids esterified into cholesteryl esters and phospholipids affect Toll-like receptor-4 and the NLRP3 inflammasome pathways which possess multiple important biological functions⁹. Hence, investigation of mechanisms affecting function of these oxidized products is promising and deserves further investigation⁴².

Our finding of increased oxHDL in psoriasis patients might be attributable to the PON1 function. PON1 is an enzyme bound to HDL that is one of many important determinants of the anti-oxidative properties of HDL and may serve as a marker of CVD progression. Low PON1 activity has been associated with worse prognosis for cardiovascular disease⁴³. In our study, psoriasis patients had significantly higher PON1 activity in comparison to healthy controls, likely a compensatory increase in response to greater oxHDL burden. Despite observing higher PON1 activity in the PSO subgroup, it is plausible that it may represent a dysfunctional, non-cardioprotective form. Finally, the bidirectionality in OML association with NCB could be a contingency in the face of chronicity of underlying low-grade inflammation in psoriasis patients.

Reduction in OML concurrent with a decrease in non-calcified coronary plaque burden following biological therapy for psoriasis.

We followed a subset of moderate-severe psoriasis patients never treated with a biologic (biologic naïve) to understand how modulation of skin inflammation with biologic treatment may affect OMLs and NCB. Psoriasis treatment significantly decreased inflammatory response and restored HDL function independent of lipid levels¹⁸. As anticipated, oxHDL levels decreased following treatment and oxLDL trended towards a decrease. The differential, and more significant, treatment effects on oxHDL may be explained by its heterogeneity and relative ease of alteration of its dysfunctional form with abrogation of systemic inflammation. The detected increase in plasma TG and Lp(a) levels early on during treatment (3-5 month follow up) may be due to a higher hepatic conversion of free fatty acids into TG. However, to what extent this observation relates to psoriasis specific treatment or depicts the natural history of the disease, needs future investigation. Furthermore, PSO patients on treatment were noted to have an improvement in NCB at one-year follow up, independent of traditional cardiovascular risk, validating previous work⁴⁴. The reduction in OMLs concurrent with reduction in NCB warrants careful in vitro follow up studies to understand whether these are direct effects or operating through other complementary pathways.

Given the association between plasma markers of lipoprotein oxidation and incidence of atherosclerotic disease in chronic inflammatory states, it may be of clinical utility to investigate these markers in the early cardiovascular risk assessment of patients with chronic inflammatory disease and to assess efficacy of anti-psoriatic/anti-inflammatory interventions. Furthermore, future research should attempt to expound the impact of different biologic therapies on these cardiovascular biomarkers with longer-duration follow-ups. Considering the impact of lifestyle modifications as well as intensive statin-based regimen on polyunsaturated fatty acids oxidized products, the role of OML needs to be more deeply explored in reducing residual CVD risk in psoriatic patients over time. Finally, trials with deep characterization of lipoproteins concurrent with imaging-based assessment of early atherosclerosis (e.g. non-calcified coronary plaque or vascular inflammation) should examine the comprehensive effect of biologic therapies on these lipoprotein biomarkers and whether there is subsequent effect on subclinical atherosclerosis.

Strengths and limitations.

To our knowledge, this is the first study to associate coronary plaque burden in psoriasis with OMLs. Longitudinal examination over one-year demonstrated that improvement in skin disease was associated with an improvement in oxidation-modified lipid fraction and NCB. These findings are of interest because they suggest that OML and NCB may improve with adequate anti-psoriasis therapy.

Our study is limited by small sample size as well as follow-up data and did not have randomized treatment allocation. Given the observational study design, we cannot exclude the possibility of residual confounding and are unable to derive any causal inferences. Furthermore, our study relied on a surrogate marker of coronary artery disease through CCTA as the primary outcome instead of hard CV events; however, this was consistent with our intent to understand the natural course prior to CV events. When characterizing lipoproteins and CVD, sources of bias include age, gender, hypertensive status, dyslipidemia status, smoking status and medical treatments. In our multivariable variables to understand the relationship between OMLs and coronary artery disease, we adjusted for these factors to attempt to understand whether an independent relationship existed between each OMLs and coronary artery disease. Furthermore, there are sources of bias that were not measured in our study and therefore not adjusted for in our models. These include dietary intake of specific foods, as well as detailed exercise frequency, as well as some psoriasis specific features which may be prone to recall bias (e.g. onset of psoriasis which permits psoriasis disease duration calculation). Lastly, investigating OMLs and CCTA results from healthy individuals without psoriasis and those with CVD are of great interest and should be a topic of future study in this field.

Conclusion.

In conclusion, we demonstrated that the OMLs were increased in psoriasis and were differentially associated with coronary plaque burden, especially NCB, by psoriasis severity. Furthermore, we also demonstrated that anti-inflammatory treatment of psoriasis with biologic agents led to reduction in OMLs with a reduction in lipid-rich plaque as assessed by NCB. Collectively, we demonstrated the utility of OMLs and its association with early subclinical atherosclerosis in coronary arteries. As such, future larger studies should confirm these findings and assess whether various biologic treatments lead to mitigation of early cardiovascular disease and favorable modulation of OMLs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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CONFLICT OF INTEREST AND FINANCIAL DISCLOSURES

Dr. Gelfand served as a consultant for AbbVie, AstraZeneca, Celgene Corp, Coherus, Eli Lilly, Janssen Biologics (formerly Centocor), Sanofi, Merck, Novartis Corp, Valeant, and Pfizer Inc, receiving honoraria; received research grants (to the Trustees of the University of Pennsylvania) from AbbVie, Amgen, Eli Lilly, Janssen, Novartis Corp, Regeneron, and Pfizer Inc; and received payment for continuing medical education work related to psoriasis. Dr. Gelfand is a copatent holder of resiquimod for the treatment of cutaneous T-cell lymphoma.

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Nonstandard Abbreviations and Acronyms:

LMs	Lipid mediators
OMLs	Oxidation-modified lipids

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NOVELTY AND SIGNIFICANCE

What Is Known?

- Oxidation of lipoproteins, specifically LDL, is closely linked to development of atherosclerosis.
- Inflammation contributes to the initiation and propagation of oxidation.
- Psoriasis is a chronic inflammatory skin disease associated with increased oxidative stress and atherosclerosis.

What New Information Does This Article Contribute?

- Oxidation-modified lipids including oxLDL and oxHDL were significantly elevated in psoriasis.
- Oxidation-modified lipids were differentially associated with coronary plaque burden when stratified by psoriasis disease severity beyond traditional risk factors; this relationship was not captured by traditional lipids.
- Biological therapy for psoriasis was associated with a reduction in oxHDL and with a concomitant decrease in non-calcified burden at one year.

Psoriasis adds a cumulative risk to early cardiovascular disease development in a relatively young population by affecting lipoproteins function and coronary plaque composition. Limited prognostic value of traditional lipid parameters in psoriasis subjects warrants search for novel diagnostic markers for cardiovascular disease. Considering that lipid oxidation leads to pro-inflammatory and pro-atherosclerotic gain of function, we hypothesized that psoriasis, a systemic chronic inflammatory state with impaired oxidation, might significantly contribute to this process. We found that oxidation-modified lipoproteins, specifically oxLDL and oxHDL, differentially associated with lipid-rich plaque based on psoriasis severity. Furthermore, psoriasis patients on treatment notably had reduction in oxHDL, which was associated with an improvement in lipid-rich plaque. Future investigation characterizing precise function of these oxidation-modified lipids may provide promising diagnostic platforms for effective cardiovascular disease management in psoriasis.

Figure 1.
Recruitment and follow-up scheme of study participants

Table 1.

Demographic and clinical characteristics of the study groups

Parameter	Psoriasis (n=232)	Healthy volunteers (n=20)	P
Demographics and medical history			
Age (years)	50.13 ± 12.64	40.45 ± 13.73	<0.001
Male sex, n (%)	136 (58)	12 (60)	0.90
Body mass index (kg/m ²)	29.46 ± 6.31	25.21 ± 4.92	0.002
Hypertension, n (%)	65 (28)	2 (10)	0.08
Hyperlipidemia, n (%)	105 (45)	0 (0)	<0.001
Type 2-diabetes, n (%)	25 (10)	0 (0)	0.12
Current smoker, n (%)	23 (9)	0 (0)	0.14
Lipid lowering therapy, n (%)	71 (68)	0 (0)	0.003
Clinical and laboratory values			
Systolic BP (mmHg)	122.46 ± 14.80	108.55 ± 10.47	<0.001
Total cholesterol (mg/dl)	183.18 ± 37.24	174.15 ± 34.35	0.15
Triglycerides (mg/dl)	123.01 ± 75.66	89.00 ± 26.93	0.02
HDL cholesterol (mg/dl)	56.32 ± 18.28	59.50 ± 16.71	0.23
LDL cholesterol (mg/dl)	102.37 ± 30.47	96.95 ± 28.15	0.22
Lp(a) (nmol/L)	49.73 ± 41.76	31.58 ± 27.29	0.004
ApoA1 (mg/L)	156.18 ± 31.08	158.15 ± 27.57	0.40
ApoB (mg/L)	90.51 ± 21.74	81.05 ± 16.99	0.03
ApoB / ApoA1	0.86 ± 0.60	0.53 ± 0.13	0.007
Framingham risk score	4 (1-6)	2 (1-2)	0.003
hsCRP (mg/L)	4.48 (0.80-4.22)	1.24 (0.60-1.00)	0.002
HOMA-IR	4.04 (1.58-4.73)	2.01 (1.43-2.31)	0.006
Cholesterol efflux capacity	0.96 ± 0.16	0.96 ± 0.17	0.45
Oxidation-modified lipids			
oxHDL (U/ml)	202.89 ± 175.62	176.88 ± 216.25	0.02
oxLDL (U/L)	62.68 ± 22.71	54.77 ± 16.78	0.07
oxLp(a) (nmol/L)	0.031 ± 0.10	0.001 ± 0.00	0.02
Psoriasis Severity and Treatment			
Disease duration, years	20.32 ± 13.75	N/A	N/A
PASI score	7.9 (2.8-10.0)	N/A	N/A
Systemic or biologic therapy, n (%)	86 (38)	N/A	N/A

Data represented as mean ± SD or median (IQR) for parametric and non-parametric variables respectively and as n (%) for categorical variables. P-values were derived from a single unpaired students t-test for parametric variables and Mann-Whitney U test for non-parametric variables. The Pearson's Chi-square test was used for categorical variables. P<0.05 was considered statistically significant. HOMA-IR, homeostatic model assessment of insulin resistance; hsCRP, high-sensitivity C-reactive protein; PASI, psoriasis area severity index.

Table 2.

Relationship between oxidation-modified lipids and different variables in psoriasis subjects

Variable	LDL		oxLDL		HDL		oxHDL		Lp(a)		oxLp(a)	
	β	P	β	P	β	P	β	P	β	P	β	P
Demographics												
Age	-0.13	0.001	-0.03	0.39	0.14	0.0001	0.11	0.01	0.10	0.01	0.08	0.04
Male sex	-0.003	0.94	-0.05	0.21	-0.34	0.0001	-0.14	0.0001	0.03	0.40	-0.08	0.04
Hypertension	-0.12	0.001	0.01	0.86	-0.05	0.24	0.04	0.30	0.03	0.51	0.11	0.006
Type 2-diabetes	-0.12	0.002	-0.06	0.43	-0.12	0.001	-0.14	0.0001	0.05	0.22	-0.03	0.41
Hyperlipidemia	0.03	0.37	0.08	0.03	-0.07	0.07	-0.05	0.18	0.12	0.002	0.07	0.06
Current smoker	-0.02	0.57	-0.06	0.13	-0.09	0.02	-0.05	0.19	0.05	0.24	-0.05	0.17
Clinical and Laboratory Values												
Body mass index	0.06	0.11	0.17	0.0001	-0.41	0.0001	-0.15	0.0001	0.01	0.75	-0.04	0.31
Glucose	-0.14	0.0001	-0.03	0.69	-0.16	0.0001	-0.19	0.0001	0.13	0.001	-0.01	0.82
Insulin	-0.03	0.40	0.06	0.16	-0.31	0.0001	-0.17	0.0001	-0.06	0.15	-0.03	0.42
HOMA-IR	-0.08	0.04	0.04	0.27	-0.32	0.0001	-0.21	0.0001	-0.03	0.46	-0.04	0.37
HbA1C	-0.15	0.001	0.05	0.58	-0.17	0.0001	-0.24	0.0001	0.05	0.29	0.05	0.31
hsCRP	-0.06	0.11	0.02	0.81	-0.40	0.0001	-0.02	0.58	0.01	0.86	-0.04	0.35
Cholesterol efflux capacity	0.07	0.08	0.13	0.06	0.48	0.0001	0.01	0.74	0.02	0.69	-0.06	0.13
Framingham risk score	0.09	0.01	0.09	0.03	-0.16	0.0001	0.08	0.07	0.02	0.63	0.06	0.11
Psoriasis Details												
PASI score	0.05	0.21	-0.06	0.41	-0.07	0.07	0.04	0.27	-0.02	0.66	-0.11	0.01
Systemic or biologic therapy	-0.08	0.03	0.07	0.06	0.07	0.05	-0.06	0.13	-0.11	0.007	0.09	0.02

Results reported as standardized β coefficient (P values). HOMA-IR, homeostatic model assessment of insulin resistance; hsCRP, high-sensitivity C-reactive protein; PASI, psoriasis area severity index.

Table 3.

Relationship between coronary plaque parameters and different variables in psoriasis subjects

A: Relationship between CCTA plaque parameters and traditional lipids						
Variable	TC		LDL		HDL	
	β	P	β	P	β	P
TB	-0.18	0.0001	-0.05	0.24	-0.32	0.0001
NCB	-0.18	0.0001	-0.04	0.43	-0.34	0.0001
DCB	-0.03	0.490	-0.05	0.24	0.04	0.37

B: Relationship between coronary plaque parameters and lipoprotein particles												
Variable	s_ldl_p		l_ldl_p		l_hdl_p		s_hdl_p		lm_vldl_p		s_vldl_p	
	β	P	β	P	β	P	β	P	β	P	β	P
TB	0.22	0.0001	-0.23	0.0001	-0.23	0.0001	0.06	0.18	0.08	0.09	-0.03	0.49
NCB	0.23	0.0001	-0.23	0.0001	-0.26	0.0001	0.07	0.14	0.08	0.07	-0.02	0.59
DCB	-0.04	0.37	-0.07	0.13	0.07	0.11	-0.02	0.66	-0.01	0.74	-0.03	0.56

C: Relationship between coronary plaque parameters and advance lipid phenotypes									
Variable	ApoB		Apo-A1		Lp(a)		CEC		
	β	P	β	P	β	P	β	P	P
TB	-0.02	0.60	-0.27	0.0001	-0.02	0.71	-0.28	0.0001	
NCB	-0.01	0.91	-0.30	0.0001	-0.02	0.64	-0.30	0.0001	
DCB	-0.06	0.20	0.05	0.27	0.01	0.80	0.04	0.33	

D: Relationship between coronary plaque parameters and oxidation-modified lipids						
Variable	oxLDL		oxHDL		oxLp(a)	
	β	P	β	P	β	P
TB	0.08	0.08	-0.11	0.02	0.02	0.61
NCB	0.10	0.02	-0.12	0.007	0.02	0.59
DCB	-0.06	0.18	0.03	0.50	-0.02	0.73

Results reported as standardized β coefficient (P values). TB: total burden, NCB: Non-calcified burden, DCB: Dense-calcified burden.

Table 4.

Multivariable adjusted linear regression analysis for oxidation-modified lipids in psoriasis subjects

Model	oxLp(a)		oxLDL		oxHDL		Lp(a)	
	β	P	β	P	β	P	β	P
	TB		TB		TB		TB	
Adjusted for age, sex	0.030	0.454	0.101	0.012	−0.062	0.132	−0.043	0.290
Adjusted for current smoking	0.020	0.641	0.073	0.094	−0.106	0.016	−0.015	0.718
Adjusted for FRS	0.013	0.752	0.060	0.155	−0.119	0.005	−0.026	0.533
Adjusted for BMI	0.030	0.428	−0.031	0.408	−0.042	0.271	−0.043	0.250
Adjusted for lipid lowering therapy	0.014	0.736	0.108	0.012	−0.077	0.076	−0.027	0.523
Adjusted for systemic or biologic therapy	0.028	0.525	0.076	0.083	−0.108	0.015	−0.015	0.732
Adjusted for FRS+BMI	0.023	0.523	−0.034	0.353	−0.056	0.133	−0.048	0.191
Adjusted for FRS+Lipid lowering therapy	0.009	0.820	0.095	0.025	−0.102	0.017	−0.032	0.446
Adjusted for FRS+Lipid lowering therapy+Systemic or biologic therapy	0.013	0.760	0.094	0.028	−0.101	0.020	−0.029	0.492
	NCB		NCB		NCB		NCB	
Adjusted for age, sex	0.034	0.404	0.123	0.003	−0.070	0.087	−0.042	0.298
Adjusted for current smoking	0.021	0.623	0.099	0.023	−0.119	0.007	−0.020	0.646
Adjusted for FRS	0.015	0.709	0.088	0.038	−0.130	0.002	−0.029	0.495
Adjusted for BMI	0.032	0.388	−0.010	0.771	−0.051	0.166	−0.050	0.176
Adjusted for lipid lowering therapy	0.017	0.681	0.127	0.003	−0.099	0.024	−0.028	0.508
Adjusted for systemic or biologic therapy	0.028	0.523	0.102	0.020	−0.121	0.007	−0.019	0.656
Adjusted for FRS+BMI	0.027	0.454	−0.013	0.723	−0.062	0.094	−0.053	0.143
Adjusted for FRS+Lipid lowering therapy	0.013	0.752	0.12	0.005	−0.121	0.005	−0.032	0.442
Adjusted for FRS+Lipid lowering therapy+Systemic or biologic therapy	0.015	0.716	0.12	0.006	−0.120	0.006	−0.030	0.475
	DCB		DCB		DCB		DCB	
Adjusted for age, sex	−0.024	0.563	−0.034	0.414	0.020	0.638	−0.014	0.735
Adjusted for current smoking	−0.015	0.718	−0.059	0.173	0.029	0.505	0.011	0.801
Adjusted for FRS	−0.022	0.594	−0.072	0.091	0.018	0.671	0.002	0.945
Adjusted for BMI	−0.017	0.692	−0.051	0.249	0.024	0.580	0.015	0.730
Adjusted for lipid lowering therapy	−0.025	0.550	−0.025	0.557	0.067	0.119	−0.002	0.946
Adjusted for systemic or biologic therapy	−0.009	0.838	−0.057	0.191	0.024	0.586	0.010	0.805
Adjusted for FRS+BMI	−0.026	0.545	−0.056	0.197	0.005	0.890	0.008	0.841
Adjusted for FRS+Lipid lowering therapy	−0.029	0.492	−0.047	0.266	0.051	0.227	−0.006	0.887
Adjusted for FRS+Lipid lowering therapy+Systemic or biologic therapy	−0.022	0.606	−0.048	0.262	0.051	0.236	−0.003	0.943

Results reported as standardized β value (P values). FRS-Framingham risk score, BMI-body mass index, TB: Total burden, NCB: Non-calcified burden, DCB: Dense-calcified burden.

Table 5.

Relationships between oxidation-modified lipids and coronary plaque burden in psoriasis subjects, as stratified by psoriasis disease severity and systemic or biologic treatment at baseline

Variable	oxHDL			oxLp(a)			oxLDL			Lp(a)		
	PASI<3	PASI>3	P	PASI<3	PASI>3	P	PASI<3	PASI>3	P	PASI<3	PASI>3	P
TB	214.96±4.77	198.99±13.74	0.28	0.037±0.01	0.030±0.01	0.36	61.57±2.97	62.43±1.83	0.40	47.32±5.26	49.99±3.34	0.34
	-0.111; 0.177	-0.092; 0.079		0.265; 0.001	-0.075; 0.149		0.227; 0.005	0.017; 0.750		0.034; 0.677	-0.037; 0.483	
NCB	-0.133; 0.107	-0.102; 0.051		0.237; 0.004	-0.066; 0.209		0.242; 0.003	0.045; 0.384		0.045; 0.583	-0.047; 0.369	
DCB	-0.026; 0.758	0.032; 0.536		0.076; 0.360	-0.058; 0.263		0.102; 0.217	-0.126; 0.015		-0.062; 0.450	0.036; 0.488	
Variable	PASI<10	PASI>10		PASI<10	PASI>10		PASI<10	PASI>10		PASI<10	PASI>10	
	202.88±14.25	204.74±22.60	0.47	0.036±0.02	0.020±0.01	0.15	62.89±1.87	60.31±2.74	0.23	48.61±3.24	51.14±5.74	0.35
TB	-0.160; 0.002	-0.007; 0.934		0.102; 0.043	-0.171; 0.055		0.177; 0.0001	-0.164; 0.064		-0.064; 0.204	0.074; 0.408	
NCB	-0.156; 0.002	-0.056; 0.535		0.102; 0.043	-0.179; 0.045		0.198; 0.0001	-0.135; 0.128		-0.071; 0.159	0.081; 0.368	
DCB	-0.039; 0.444	0.225; 0.011		-0.015; 0.771	-0.025; 0.786		-0.021; 0.683	-0.200; 0.023		0.018; 0.725	-0.004; 0.963	
	Treatment			Treatment			Treatment			Treatment		
Variable	YES	NO		YES	NO		YES	NO		YES	NO	
	211.78±15.53	189.03±19.03	0.18	0.024±0.05	0.046±0.02	0.06	60.99±1.90	64.36±2.68	0.15	51.96±3.72	44.69±4.21	0.11
	Treatment			Treatment			Treatment			Treatment		
Variable	YES	NO		YES	NO		YES	NO		YES	NO	
PASI score	7.25±0.98	8.27±0.63	0.18	7.25±0.98	8.27±0.63	0.18	7.25±0.98	8.27±0.63	0.18	7.25±0.98	8.27±0.63	0.18
TB	-0.105; 0.062	-0.111; 0.120		-0.129; 0.021	0.260; 0.0002		-0.065; 0.240	0.320; 0.0001		-0.008; 0.892	-0.032; 0.649	
NCB	-0.119; 0.034	-0.122; 0.087		-0.130; 0.020	0.255; 0.0003		-0.061; 0.273	0.373; 0.0001		-0.010; 0.861	-0.039; 0.584	
DCB	0.017; 0.760	0.048; 0.502		-0.040; 0.474	0.034; 0.639		0.039; 0.485	-0.240; 0.001		-0.002; 0.967	0.030; 0.674	

Data represented as mean ± SE or median (IQR) for parametric and non-parametric variables respectively and as n (%) for categorical variables. P-values were derived from a single unpaired students t-test for parametric variables and Mann-Whitney U test for non-parametric variables. Pearson correlation coefficients represented as rho values, (P values). PASI <3 – mild, 3-10 – moderate, >10 – severe. TB: Total burden, NCB: Non-calcified burden, DCB: Dense-calcified burden, PASI: Psoriasis area severity index.

Table 6.

Characteristics of a subset of moderate-severe, biologic naïve psoriasis patients

Parameter	Baseline (n=20)	3-5 months (n=20)	P
Clinical and laboratory values			
Total cholesterol (mg/dl)	180.35 ± 34.29	186.30 ± 44.85	0.11
Triglycerides (mg/dl)	88.90 ± 41.45	103.05 ± 54.79	0.02
HDL cholesterol (mg/dl)	59.05 ± 12.50	59.95 ± 21.10	0.39
LDL cholesterol (mg/dl)	103.50 ± 28.91	105.45 ± 33.47	0.29
Lp(a) (nmol/L)	61.58 ± 56.80	65.78 ± 62.25	0.32
ApoA1 (mg/L)	158.60 ± 20.48	158.60 ± 20.48	1.00
ApoB (mg/L)	89.30 ± 20.37	91.50 ± 20.37	0.20
ApoB / ApoA1	0.83 ± 0.57	0.59 ± 0.16	0.04
Framingham risk score	2 (1-2)	3 (1-2.8)	0.37
hsCRP (mg/L)	8.25 (0.80-10.70)	5.71 (0.75-5.80)	0.02
HOMA-IR	3.56 (1.19-3.15)	3.84 (1.39-5.25)	0.48
Oxidation-modified lipids			
oxHDL (U/ml)	203.79 ± 88.40	116.36 ± 85.03	0.0005
oxLDL (U/L)	64.23 ± 18.45	60.45 ± 16.17	0.11
oxLp(a) (nmol/L)	0.01 ± 0.03	0.007 ± 0.02	0.33
Psoriasis Severity and Treatment			
Disease duration (years)	21.30 ± 13.41	21.47 ± 14.20	0.02
PASI score	17.24 (8.05-24.25)	3.96 (1.6-6.2)	0.0001
Systemic or biologic therapy, n (%)	0 (0)	20 (100)	N/A
Coronary characterization			
	Baseline (n=20)	1-year (n=20)	
Total plaque burden (×100), mm ²	1.09 ± 0.40	1.00 ± 0.31	0.01
Dense-calcified plaque burden (×100), mm ²	0.05 ± 0.07	0.04 ± 0.05	0.08
Non-calcified plaque burden (×100), mm ²	1.04 ± 0.44	0.95 ± 0.32	0.03

Data represented as mean ± SD or median (IQR) for parametric and non-parametric variables respectively and as n (%) for categorical variables. P values were derived from a paired t test for parametric variables and the Wilcoxon signed rank test for non-parametric variables. The McNemar's test was used for categorical variables. P<0.05 was considered statistically significant. HOMA-IR, homeostatic model assessment of insulin resistance; hsCRP, high-sensitivity C-reactive protein; PASI, psoriasis area severity index.