Original Article

Comprehensive lipid tetrad index, atherogenic index and lipid peroxidation: Surrogate markers for increased cardiovascular risk in psoriasis

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ABSTRACT

Background and Objectives: Recently, the concept of "psoriatic march" has come to the fore, in which chronic cutaneous inflammation in psoriasis leads to systemic inflammation which, in conjunction with increased oxidative stress, triggers a cascade of events resulting in increased cardiovascular risk in patients with severe psoriasis. We, therefore, decided to study the levels of some biochemical cardiovascular risk markers: lipid peroxidation (malondialdehyde), lipoprotein (a), lipid indices and atherogenic index, in patients with psoriasis and their association with disease severity. **Methods:** Fortyfive patients with psoriasis and 45 age and gender-matched healthy controls were included in this cross-sectional study. Disease severity was assessed by the Psoriasis Area Severity Index (PASI). Serum malondialdehyde, lipoprotein (a) and fasting lipid profile were estimated in all study subjects. Lipoprotein ratios were computed using standard formulae. Atherogenic index was calculated as ratio of lipoprotein (a)/high-density lipoprotein. **Results:** In psoriasis, we observed significantly higher levels of malondialdehyde, total cholesterol, low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, lipoprotein (a), lipid ratios, atherogenic index and comprehensive lipid tetrad index, compared to controls. These levels were directly proportional to disease severity. Serum levels of malondialdehyde correlated positively with serum lipoprotein (a), comprehensive lipid tetrad index and atherogenic index. **Limitations:** Different morphological types of psoriasis were not included and follow-up post-therapy was not done. A larger sample size would have validated the results further. **Conclusion:** Our results indicate that psoriasis, especially the severe variants, are associated with increased oxidative stress and dyslipidemia, which correlate positively with atherogenic index and hence, an increased cardiovascular risk.

Key words: Dyslipidemia, Framingham risk score, oxidative stress, psoriasis, psoriasis area severity index

INTRODUCTION

Psoriasis is an immune-mediated skin disease characterized by hyperproliferation of keratinocytes which is initiated and maintained by inflammatory mediators.[1] Psoriasis, which was primarily considered a cutaneous disease, is recently being identified as an associate of systemic inflammation.[2] There is a complex network of inflammatory and immune cells, cytokines, chemokines and growth factors, all of which interact with one another to initiate a cascade

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of inflammatory events resulting in T-cell infiltration in the epidermis and dermis.[3-6] Recently the concept of "psoriatic march" has been proposed, in which chronic cutaneous inflammation in psoriasis leads to systemic inflammation, which, in conjunction with increased oxidative stress triggers a cascade of events including oxidative stress, dyslipidemia, endothelial dysfunction and insulin resistance which increases the risk of cardiovascular complications in these patients.[7-9]

Recent studies have shown a rise in plasma lipid and lipoprotein levels with an increase in the levels of triglycerides and cholesterol in subjects with psoriasis, compared to controls.[10,11] It has been observed that patients with psoriasis have a disturbance in lipid metabolism and a predisposition for atherosclerosis.[12] This alteration in lipid profile is due to the inflammatory milieu maintained by the cytokines,[13,14] although there are some reports which show a normal lipid profile in psoriasis.[15] Low-density lipoprotein, on oxidation, induces monocyte infiltration and smooth muscle proliferation and favors atherosclerotic plaque formation.[16] High-density lipoprotein is involved in reverse cholesterol transport and inhibition of monocytic infiltration and thus suppresses atherogenicity.[17] Thus, atherogenic dyslipidemia has been linked to the inflammatory process in psoriasis.

Similarly, it is thought that oxidative stress plays a major role in enhancing the inflammatory process of psoriasis. There is an imbalance between the generation and removal of reactive oxygen species due to increased free radical generation and defective scavenging mechanisms.[18-21] This contributes to increased oxidant load and thus, increased cell damage by causing lipid peroxidation of cell membranes.[22-25] Malondialdehyde, which is a product of lipid peroxidation, is considered a marker of oxidative stress and lipid peroxidation.[26,27] Some previous studies in a North Indian population have shown raised malondialdehyde levels in psoriatic patients with co-morbidities like hypertension and diabetes.[28,29]

Another important marker for cardiovascular risk in the atherosclerosis-prone South Indian population is lipoprotein (a), a form of low density lipoprotein with apolipoprotein B100 and apolipoprotein (a) attached by a disulfide bond which is also susceptible to lipid peroxidation. Lipoprotein (a) has a structural homology with plasminogen, and also regulates synthesis of plasminogen activator inhibitor-1. It has a dual role in being thrombogenic and atherogenic, and thus increases cardiovascular risk.[30] A study by Burman *et al*. from North India suggested that lipoprotein (a) is an important marker of cardiovascular disease.[31] Another study in the North Indian population identified significantly raised levels of lipoprotein (a), alongwith a high LDL: HDL (low-density lipoprotein: high-density lipoprotein) cholesterol ratio, though no significant association was found between the LDL: HDL cholesterol ratio and lipoprotein (a) levels.[32]

Comprehensive lipid tetrad index magnifies the subtle abnormalities of the various atherogenic and anti-atherogenic lipoproteins and is derived by multiplying the three commonly measured lipids directly associated with cardiovascular disease and dividing the product by high-density lipoprotein (which is inversely associated with cardiovascular disease), i.e., [total cholesterol × triglycerides × lipoprotein (a)]/high-density lipoprotein. A study by Singh *et al*. identified comprehensive lipid tetrad index as a stronger predictor of coronary artery disease in North Indian subjects, compared to other risk factors and lipid parameters.[33] Atherogenic index, defined as the ratio of lipoprotein (a) to high-density lipoprotein, has also been found to be a good indicator of the balance of pro-/anti-atherogenic forces, and hence, of cardiovascular risk.

In this study, we undertook a comparision of the malondialdehyde, lipoprotein (a), lipoprotein ratios, comprehensive lipid tetrad index and atherogenic index in patients with psoriasis, and in controls, and their correlation with disease severity.

METHODS

This was a cross-sectional study involving two groups. Forty-five patients with psoriasis vulgaris attending the psoriasis clinic of Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER) and 45 age and gender-matched healthy volunteers were recruited for the study after obtaining written informed consent. Ethical approval was obtained from the Institute's Human Ethics Committee (approved as proposal no. IEC/SC/2012/4/106 dated December 8, 2012). The study protocol conformed to the ethical guidelines of the declaration of Helsinki.

Sample size estimation

Sample size was estimated from serum lipoprotein (a) values. Mean level of lipoprotein (a) among healthy Indians was 19.4 ± 4.6 mg/dl.[34] A previous study in Italy on the level of serum lipoprotein (a) of psoriatics, as compared to normal controls, found a magnitude of difference of 56 per cent.[35] However, we assumed a more conservative margin of difference of 15% in calculating the sample size. In order to detect this difference with 80% power at 5% level of significance, the minimum sample size required for the study was estimated as 45 in each group (cases and controls). This was calculated using the Software "PS power and sample size program version 3.0.43" (Vanderbilt University, Tennessee, USA).

Study population and work-up

Consecutive patients with psoriasis vulgaris, attending the dermatology clinic of our hospital, a tertiary care centre in South India, who satisfied the inclusion and exclusion criteria, were enrolled as cases, and age and gender-matched healthy volunteers were taken as controls. The exclusion criteria were designed stringently to eliminate confounders and to exclude study subjects with conditions that could affect our study parameters. Patients on any medication for the last one month prior to recruitment, or having malignancies, hepatic and renal disease, diabetes mellitus, morbid obesity (body mass index >30 kg/m^2), inflammatory disease and pregnancy were excluded from the study. Clinical and anthropometric parameters and existence of co-morbidities and treatment details were recorded in a predesigned proforma. In all patients with psoriasis, the disease severity was assessed by psoriasis area severity index (PASI) score.[36] The scoring for each patient was done independently by two dermatologists and the mean of the values taken for assessing the disease severity.

Cardiovascular risk assessment

Framingham risk score predicts a person's chance of having a heart attack in the next 10 years. This tool is designed for adults aged 20 and older who do not have heart disease or diabetes. Although not the ideal tool for calculating cardiovascular risk in Indians, we used this in the absence of any other established standard scoring system for cardiovascular risk in the atherosclerosis-prone South Indian population.

Framingham risk score for cardiovascular risk assessment was calculated in all study subjects using the standard formula.[37]

Assay of study parameters

Five ml of venous blood was drawn from the antecubital vein, after a fasting period of 12 hours. Serum was separated from the blood within 30 min and routine biochemical investigations like lipid profile (total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein-cholesterol, very low-density lipoprotein cholesterol) were estimated in all study subjects using standard methods using reagent kits in a well-calibrated Olympus AU400 fully automated clinical chemistry analyzer. Lipoprotein (a) was assessed using immunoturbidimetric assay kit from Tulip Diagnostics, Chennai, India. Lipoprotein ratios and comprehensive lipid tetrad index were computed using standard formulae. Atherogenic index was calculated as the ratio of lipoprotein (a) to high-density lipoprotein levels. Malondialdehyde was estimated by the method of Agarwal and Chase, using high-performance liquid chromatography (SP-20A HPLC system, Shimadzu, Japan).[38]

Statistical analysis

Statistical analysis was performed using IBM SPSS statistics version 20.0 for windows (Armonk, NY: IBM Corp.). Baseline characteristics of cases and controls were analyzed using descriptive statistics. The normality of continuous data was assessed by the Kolmogorov–Smirnov test. The data were described as mean ± standard deviation. Comparison of the various parameters between cases and controls was done by independent Student's *t*-test for parametric data and Mann–Whitney U-test for non-parametric data. The levels of the various biochemical parameters were correlated with psoriasis area severity index (PASI), using Spearman rank correlation. To assess the effects of confounders on the study parameters, a multivariate linear regression analysis was performed with malondialdehyde and lipoprotein (a) as dependent variables. Analysis was carried out at 5% level of significance and $P < 0.05$ was considered as statistically significant.

RESULTS

Fortyfive patients with psoriasis vulgaris and 45 healthy controls were included in the study. The mean duration of psoriasis was 44.38 ± 61.74 months. All 45 patients had chronic plaque psoriasis. Twelve (26.7%) patients with psoriasis had co-existent psoriatic arthritis. The mean PASI was 13.97 ± 8.28. The baseline characteristics between cases and controls were comparable. In this study, we found

that the psoriasis patients had an intermediate to high Framingham risk score as opposed to the controls, who had a low Framingham risk score ($P = 0.016$) [Table 1].

The baseline routine biochemical parameters between cases and controls were comparable, except for significantly higher serum levels of total cholesterol, low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol among cases, when compared to that of controls [Table 2]. It was also observed that patients with psoriasis had significantly higher levels of lipoprotein ratios, total cholesterol/high density lipoprotein, low-density lipoprotein/high-density lipoprotein, non-high-density lipoprotein/high-density lipoprotein and comprehensive lipid tetrad index, when compared to controls [Table 3]. We also observed that patients with psoriasis had elevated levels of malondialdehyde, lipoprotein (a) and atherogenic index, as compared to controls [Table 4]. Psoriasis severity as assessed by PASI, correlated positively with malondialdehyde, lipoprotein (a) and atherogenic index [Figures 1-3]. Serum levels of malondialdehyde correlated positively with comprehensive lipid tetrad index ($r = 0.359$, $P < 0.001$), lipoprotein (a) ($r = 0.572$, $P < 0.001$) and atherogenic index ($r = 0.518$, $P < 0.001$).

To assess the effects of confounders on the study parameters, a multivariate linear regression analysis was performed with malondialdehyde and lipoprotein (a) as dependent variables. In both the models, it was observed that psoriasis was an independent risk factor in each model, after adjusting for age, total cholesterol, atherogenic index, low-density lipoprotein and non-high-density lipoprotein.

Table 1: Comparison of baseline characteristics between cases and controls

Parameter	Mean±SD		*P* (unpaired *t*-test)
	Cases (*n*=45)	Controls (*n*=45)	
Age (years)	44.87±14.30	42.56±11.34	0.40
Gender (males:females)	36:9	36:9	-
BMI	22.88±3.41	22.96±2.21	0.91
Waist:Hip ratio	0.932±0.06	0.934±0.038	0.86
Smokers	14 (31.1%)	15 (33.3%)	0.75
Alcoholism	18 (40%)	17 (37.7%)	0.82
Framingham risk score			
Low	30 (66.7%)	39 (86.7%)	0.016*
Intermediate	13 (28.9%)	6 (13.3%)	
High	2 (4.4%)	0 (0%)	

*Chi-square test. BMI: Body mass index, SD: Standard deviation

Table 2: Comparison of lipid profile between cases and controls

Parameter	Mean±SD		*P* (unpaired *t*-test)
	Cases (*n*=45)	Controls (*n*=45)	
Total cholesterol (mg/dl)	160.38±36.23	145.33±23.53	0.02
Low-density lipoprotein cholesterol (mg/dl)	99.44±34.91	84.35±25.86	0.02
Very low-density lipoprotein cholesterol (mg/dl)	25.11±9.23	23.16±4.99	0.22
High-density lipoprotein cholesterol (mg/dl)	35.82±5.92	37.82±7.12	0.15
Triglycerides (mg/dl)	125.56±46.13	115.80±24.94	0.22
Non-high-density lipoprotein cholesterol (mg/dl)	124.56±37.44	107.51±24.43	0.01

SD: Standard deviation

DISCUSSION

Psoriasis is a systemic inflammatory disease with concomitant co-morbidities. It is known that patients with severe forms of psoriasis have a reduced life expectancy which might be due to cardiovascular complications such as myocardial infarction or stroke. In the present study, we found a statistically significant increase ($P = 0.016$) in the Framingham risk score in subjects with psoriasis in comparison with controls, indicating a significantly higher cardiovascular risk. How exactly psoriasis and its co-morbidities are pathophysiologically linked is poorly understood. The disease has been associated with oxidative stress, abnormal lipid metabolism and a high frequency of cardiovascular events resulting in increased morbidity and mortality.

The skin is continuously exposed to ultraviolet radiation and other environmental stress, resulting in oxidative injury.[3,4] There are several studies investigating the oxidant/antioxidant status in psoriasis and it has been suggested that increased reactive oxygen species and deficient antioxidant system is responsible for the pathogenesis of psoriasis.[19-22] Increased oxidative stress in psoriasis also increases the risk of atherosclerosis leading to cardiovascular events.[25]

Abnormalities in lipid metabolism may be another important contributory factor in the pathogenesis of psoriasis. There are many reports showing increased pro-atherogenic lipid profile, resulting in increased cardiovascular events.[10-14] Chronic inflammation, the

Table 3: Comparison of lipid ratios and indices between cases and controls

Parameter	Mean±SD		*P* (unpaired *t*-test)
	Cases (*n*=45)	Controls (*n*=45)	
Total cholesterol/high-density lipoprotein	4.63±1.51	4.02±1.31	0.01
Triglycerides/high-density lipoprotein	3.64±1.61	3.19±1.01	0.29
Low-density lipoprotein/high-density lipoprotein	2.90±1.33	2.38±1.205	0.03
Non-high-density lipoprotein/high-density lipoprotein	3.63±1.51	3.02±1.32	0.04
Comprehensive lipid tetrad index	16267.15±9115.52	9769.77±5228.86	<0.001

SD: Standard deviation

Table 4: Comparison of study parameters between cases and controls

Parameter	Mean±SD		*P* (unpaired *t*-test)
	Cases (*n*=45)	Controls (*n*=45)	
Malondialdehyde (μmol/ml)	13.34±3.41	7.56±1.42	<0.001
Lipoprotein (a) (mg/dl)	28.02±9.14	20.79±7.01	<0.001
Atherogenic index	0.80±0.30	0.56±0.25	<0.001

SD: Standard deviation

hallmark of psoriasis, and paradoxically, treatment of psoriasis, may both result in dyslipidemias. Conversely, there are certain studies showing a normal lipid profile.[15] In our study, patients with psoriasis had significantly higher levels of lipoprotein ratios (total cholesterol/high-density lipoprotein, low-density lipoprotein/ high-density lipoprotein, non-high-density lipoprotein/high-density lipoprotein and comprehensive lipid tetrad index) and atherogenic index, when compared to controls, suggesting the presence of atherogenic dyslipidemia in psoriasis. These findings are in concordance with the observations of Kadam *et al*., Jyothi *et al*. and Samuel and Murari.[20,22,23]

We also noted elevated levels of lipoprotein (a) and malondialdehyde in psoriatics as compared with controls. Kadam *et al*. also observed a significant increase in the malondialdehyde levels in psoriasis patients as compared with healthy controls.[20] A study by Relhan *et al*., showing lower plasma malondialdehyde levels in psoriasis patients in remission than during the active phase, also supports the view that oxidative damage plays an important role in etiopathogenesis of psoriasis.[26] However, Yildirim *et al*., in their study on 30 patients with psoriasis observed no significant difference in malondialdehyde levels between cases and controls.[24] The malondialdehyde levels did not correlate with the severity of psoriasis in their study.

Recently, there has been a focus on lipoprotein (a), comprehensive lipid tetrad index and atherogenic index

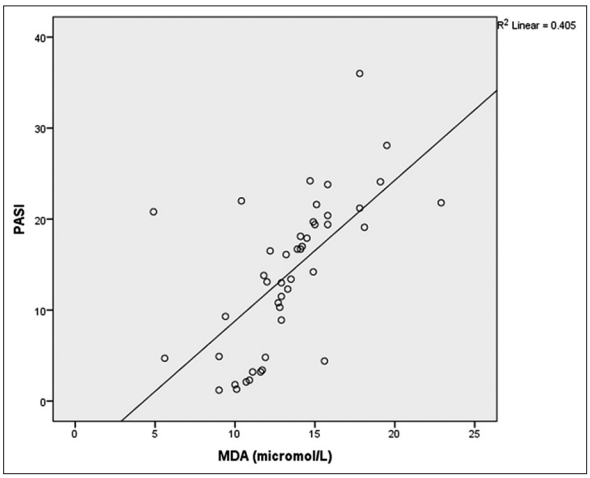

Figure 1: Correlation between malondialdehyde (MDA) and psoriasis area severity index (PASI) (r = 0.64, P < 0.001)

as markers of cardiovascular risk.[30-33] Modifications of plasma lipids and an increase in the levels of biochemical markers of lipid peroxidation have been reported in psoriasis, suggesting a relationship between the disease, lipoproteins and oxidative damage.[15,35,39] It has also been demonstrated that lipoprotein (a) is susceptible to lipid peroxidation and could be involved in atherogenesis through accumulation in the vessel wall leading to the recruitment of macrophages and finally, the development of atherosclerotic plaques.[30] Lipoprotein (a) has a structural homology with plasminogen and also regulates the synthesis of plasminogen activator inhibitor-1 and has a dual role in being thrombogenic and atherogenic and hence increases cardiovascular risk.[30]

In our study, we observed significantly higher levels of lipoprotein (a) in patients with psoriasis when compared to controls and these levels correlated positively with the disease severity. In agreement with our studies, Uyanik *et al*., showed that serum lipoprotein (a) and triglycerides were significantly higher in psoriatic patients.[15] Similarly, Ferretti *et al*., in their study on 23 patients with psoriasis observed a positive correlation between lipoprotein (a) levels

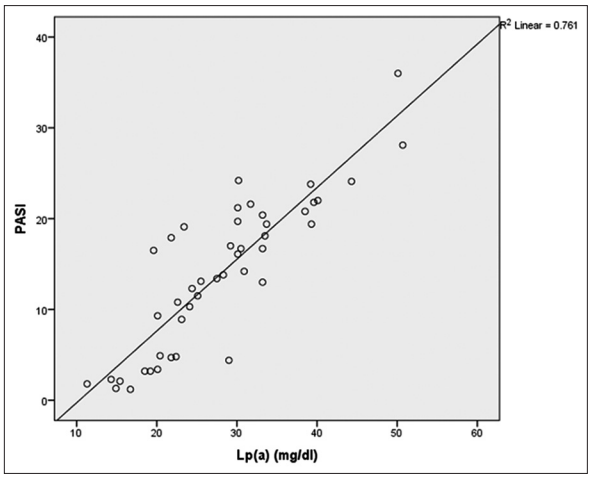

Figure 2: Correlation between lipoprotein (a) (Lp [a]) and psoriasis area severity index (PASI) ($r = 0.87$, $P < 0.001$)

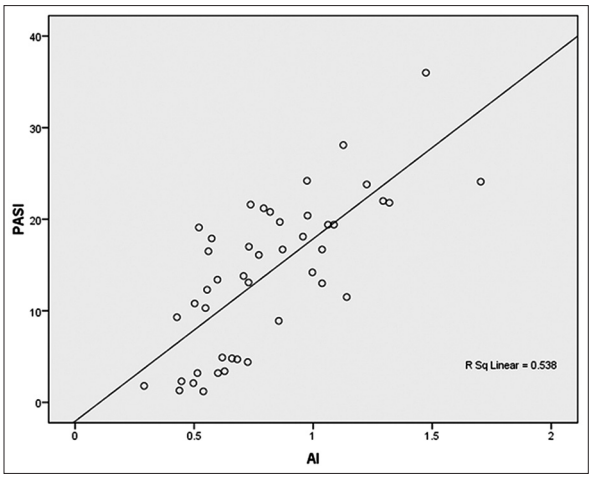

Figure 3: Correlation between atherogenic index (AI) and psoriasis area severity index (PASI) ($r = 0.73$, $P < 0.001$)

and markers of lipid peroxidation in psoriasis, when compared to controls, suggesting that subjects with higher levels of lipoprotein (a) are more susceptible to lipoprotein peroxidation.[35] Pietrzak *et al*. also showed that malondialdehyde and lipoprotein (a) levels were significantly higher in patients with psoriasis, than in the control group.[39] Nemati *et al*., on the other hand, observed that there were no significant statistical differences in serum levels of lipoprotein (a), triglycerides, very low-density lipoprotein cholesterol and high-density lipoprotein cholesterol between the two groups.[40]

We found a positive association between malondialdehyde and comprehensive lipid tetrad index, indicating that the oxidative stress is directly associated with the total burden of dyslipidemia in psoriatic subjects. Further, we observed that malondialdehyde, lipoprotein (a) and atherogenic index correlated positively with each other, as well as with disease severity, thus showing an association with increased cardiovascular risk in psoriatic patients.

The combined effect of atherogenic dyslipidemia, oxidative stress and systemic inflammation in psoriasis leads to its co-morbidities, through a cascade of events referred to as "psoriatic march" which ultimately leads to endothelial dysfunction, insulin resistance and cardiovascular disease. As psoriasis and cardiovascular disease are both T helper 1/T helper 17 mediated inflammatory diseases with a common pathogenesis, psoriasis can be considered as an individual risk factor for development of cardiovascular events.

Our study had a few limitations. The major limitation was that in the absence of other standard scoring systems for measuring cardiovascular risk in the Indian population, we used the Framingham heart risk score, though it is not the ideal tool in this context. Secondly, a relatively smaller sample size, involving only 90 study subjects, was used in the study. A larger sample size would have validated our results further. Finally, different morphological types of psoriasis were not included and follow-up after treatment was not undertaken.

CONCLUSION

Our results suggest that there is interplay between atherogenic dyslipidemia and oxidative stress in patients with psoriasis, especially with severe disease, suggesting that they are more prone to develop cardiovascular disease (as indicated by higher Framingham heart risk score) in comparison with healthy controls. Elevated comprehensive lipid tetrad index, atherogenic index and lipid peroxidation, especially in severe disease, may be used as surrogate indicators for increased cardiovascular risk in psoriasis, as it is associated with co-morbidities which cascade to lead onto cardiovascular morbidity. Thus, early anti-oxidant supplementation and screening and treatment of the atherogenic dyslipidemia might be warranted in psoriatics to mitigate the development of atherosclerosis and its complications. Furthermore, these simple indices may be useful in the clinics for cardiovascular risk assessment, thus obviating the need for expensive biomarkers which can be restricted to research settings.

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Conflicts of interest

There are no conflicts of interest.

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