Original Article

Cardiovascular and Metabolic Risk Assessment in Patients with Lichen Planus: A Tertiary Care Hospital-based Study from Northern India

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Abstract

Background: The association between lichen planus (LP) and cardiovascular disease (CVD) risk factors has been demonstrated in previous reports. However, the evidence of CVD risk factors in Indian patients with LP is limited. **Objective:** To compare CVD risk factors in LP patients and healthy controls. **Methods:** We performed a cross-sectional study on 122 subjects, 61 LP patients, and 61 controls who visited the outpatient clinic of the dermatology department of a tertiary care hospital. Patients with skin diseases known to be associated with CV risk, pregnant, and lactating women were excluded from the study. CVD risk factors were compared between LP cases and controls using anthropometric measures, hemodynamic and metabolic parameters, and inflammatory marker (ESR). **Results:** The proportion of metabolic syndrome (MS) was significantly higher in LP patients than the controls (29.5% vs. 9.8%, odds ratio [OR] 3.83; 95% confidence interval [CI] 1.40–10.50; P = 0.006). The proportion of dyslipidemia was also significantly higher in LP patients (70.5% vs. 42.6%; P = 0.002). LP patients had a high proportion of obesity (P = 0.004), hypertension (P = 0.004), impaired fasting glucose (P = 0.025), and raised ESR (P = 0.006) as compared to controls. A multivariate regression model demonstrated that dyslipidemia and obesity were significantly associated with LP even after controlling for confounders such as age, gender, sedentarism, dietary habits, alcohol, and impaired fasting glucose. There was no significant association between the extent of LP and the proportion of MS or dyslipidemia. **Conclusion:** The present study found a significant association of LP with individual CVD risk factors as well as MS.

Keywords: *Cardiovascular risk factors, dyslipidemia, inflammation, Lichen planus, metabolic syndrome, obesity*

Introduction

Lichen planus (LP) is a chronic idiopathic, self-limiting papulosquamous, and immune-mediated inflammatory disease that can affect the skin, nails, hair, and mucous membranes. The constellation of clinical symptoms and skin findings that characterize LP can be well summarized by the "six P's": *pruritic, purple, polygonal, planar, papules, and plaques*.[1,2] It affects people of all ages, and no predilection of gender or ethnicity is evident. The overall prevalence of LP is less than 1% in the general population, and in India, the prevalence varies between 0.38 and 1.4%.[2] The exact etiology of LP remains obscure, and its pathogenesis is proposed to involve three sequential steps, which begin with recognition of LP specific antigen followed by cytotoxic lymphocyte activation and culminating in keratinocyte apoptosis.[3] This creates a pro-inflammatory and pro-thrombotic state, which disrupts lipid metabolism, insulin signaling, and adipogenesis.[4] The lipid alterations linked to chronic inflammation in LP participate in the increase of cardiovascular disease (CVD) risk factors associated with dyslipidemia and other components of metabolic syndrome (MS).[5] Systemic inflammation is a known risk factor for CVD as persistent inflammation has been postulated to accelerate atherosclerosis and atrial fibrillation, which are associated with adverse CV events.[6]

In the past few decades, many inflammatory dermatological diseases such as psoriasis, androgenic alopecia, and systemic lupus erythematosus have been demonstrated to have increased CVD risk factors.[7,8] The association of psoriasis with CVD risk factors, in particular, has been widely investigated since 2004 and

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is found to be the strongest among other skin diseases.[8,9] LP, a chronic inflammatory disease morphologically akin to psoriasis, has also drawn the attention of researchers toward investigating the same associations. Several recent studies have observed metabolic derangements and other CVD risk factors in LP.[5,10-15] Many of these studies are retrospective and focus on evaluating metabolic risks only and some also lack a control group.[10,11,16,17] Furthermore, our knowledge of CVD risk factors in patients with LP remains limited, and there is a paucity of studies assessing CVD risk factors in Indian patients with LP.

Methods

Study design

This was a hospital-based cross-sectional study conducted over a period of 1 year from 2015 to 2016 in the post-graduate department of Dermatology of a tertiary care hospital in northern India.

Study population

The study population consisted of 122 subjects aged ≥18 years, 61 LP patients (cases), 61 age (±5 years) and gender-matched controls, recruited consecutively from the outpatient clinic of the dermatology department. Controls were enrolled from among the patients visiting the outpatient clinic for other skin diseases. The inclusion and exclusion criteria were designed stringently to eliminate confounders and to exclude study subjects with conditions that could affect our study parameters. Inclusion criteria were: all clinically diagnosed and histopathologically confirmed cases of LP, age ≥18 years, and willing to participate in the study. Exclusion criteria were lichenoid drug eruptions, patients on current treatment, and those who had received systemic corticosteroids, retinoids, or methotrexate within the last 1 month, other skin diseases associated with CVD risk such as psoriasis, androgenetic alopecia, pregnant, and lactating women, those with systemic inflammatory involvement e.g., immunobullous disorders, connective tissue diseases, thyroid disease, familial hyperlipidemia, nephritic syndrome, and chronic renal failure, and subjects with positive family history of hypertension and diabetes. The source population for cases and controls was the same.

Sample size estimation

Sample size of the study population was estimated according to the prevalence of CV risk factor reported in LP patients in a previous study.[11] The sample size calculation was performed using the OpenEpi (Version 3) with 95% confidence interval; power of study 80%; control to case ratio 1:1; rate of exposed controls: 33% and OR 3.71.[11] To detect a significance level with these parameters, it was required to enroll a minimum of 51 subjects per group.

Collection of data: Work-up and cardiovascular risk assessment

After obtaining informed consent from the subjects, a detailed history was taken pertaining to age, gender, occupation and duration of disease, treatment history, previous drug use (gold salts, beta-blockers, thiazide diuretics, furosemide, etc.), personal or family history of CVD, smoking habits, alcohol consumption, dietary habits (vegetarian/non-vegetarian), and lifestyle (sedentary/non-sedentary). General physical and systemic examination was performed. Sites involved and the morphologic type of LP were recorded. In the absence of any disease-specific scoring system, LP patients were assessed according to extent of involvement as (1) cases with skin involvement only and (2) cases with skin and extracutaneous involvement.

Biometric data such as weight, height, hip, and waist circumference (WC) were measured and anthropometric indices: body mass index (BMI), waist-to-hip ratio (WHR), and waist-to-height ratio (WHtR) were calculated. BMI was used to classify generalized obesity and subjects with BMI ≥25 were categorized as obese.[18] Abdominal adiposity (central obesity) was defined according to WC (WC ≥90 cm for men and WC ≥80 cm for women),[19] WHR (WHR >0.9 for men and WHR >0.8 for women),[20] and WHtR (WHtR >0.50).[21] Blood pressure was recorded as the average of two measurements after subjects had been sitting for 5 min.

Routine investigations such as hemogram, liver, and renal function tests were performed in all cases. The following investigations were performed in both cases and controls after 12-h of overnight fasting: serum total cholesterol (TC), triglycerides (TGs), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), very-low-density lipoprotein cholesterol (VLDL-C), erythrocyte sedimentation rate (ESR), and fasting blood sugar (FBS). In addition, lipoprotein/atherogenic ratios: Castelli's risk indices: (CR-I=TC/HDL-C and CR-II=LDL-C/HDL-C), atherogenic index of plasma (AIP=log (TGs/HDL-C), and atherogenic coefficient (AC=TC-HDL-C/HDL-C) were computed.

Impaired fasting glucose (IFG), hypertension, and dyslipidemia were defined according to the National Cholesterol Education Program's Adult Treatment Panel III (NCEP-ATP III) guidelines,[22] and diagnosis of MS was according to Harmonization criterion for Asian-Indian population [Table 1].[19,23]

Statistical analysis

The data were analyzed using SPSS 18.00 (Statistical Package for Social sciences; SPSS Inc., Chicago, IL, USA) for windows. Baseline characteristics of the subjects were analyzed using descriptive statistics. Qualitative and nominal variables were measured as frequency and percentages,

and χ^2-test was applied for comparison. The Fisher's exact test was used where applicable. The quantitative variables with normal distribution were measured as mean ± standard deviation (±SD), and non-normal data were reported as median (interquartile range). The comparison of means/medians between two groups was done using the two-sample independent *t* test for normally distributed variables, and for non-normally distributed variables, Mann-Whitney U test was used. Histograms, skewness/kurtosis, and the Shapiro-Wilk test were used to examine the normality of the data distribution and the Levene's test to study the variance. Correlation between variables was analyzed using Pearson and Spearman's correlation coefficient. Binary logistic regression models (Enter method), obtaining estimates adjusted odds ratio (OR), and their 95% confidence intervals were used to measure the association between LP and CV risk factors in a multivariate analysis. A probability value $P < 0.05$ was considered significant in all analyses, and all *P* values were two-sided.

Table 1: Diagnostic criteria for metabolic syndrome as per the NCEP-ATP III and Harmonization guidelines

Risk factor	NCEP-ATP (III)	Harmonization
Central obesity		
Men	>102 cm	≥90 cm
Women	>88 cm	≥80 cm
Impaired fasting glucose (Hyperglycaemia)	≥100 mg/dl	≥100 mg/dl
Hypertriglyceridemia	≥150mg/dl	≥150mg/dl
Low HDL cholesterol	<40 mg/dl	<40 mg/dl
Men	<50 mg/dl	<50 mg/dl
Women		
Elevated blood pressure	≥130/≥85 mmHG	≥130/≥85 mmHG
Diagnostic criteria	3/5 risks	3/5 risks

Ethics

The study was conducted after ethical approval was obtained from the Institute's Ethics Committee. The study protocol conformed to the ethical guidelines of the declaration of Helsinki.

Results

A total of 61 cases of LP and 61 age- and gender-matched controls were included in the study with 36 (59%) males and 25 (41%) females in each group. The male to female ratio was 1.44:1. Majority of the patients were in the age group of 31–40 years, both in cases 16 (26.2%) and controls 18 (29.5%). Age of the cases ranged from 20 to 80 (Median: 30) years and that of controls from 20 to 75 (Median: 40) years.

The mean duration of disease was 13.08 ± 16.03 (Median: 5) months with majority 24 (39.3%) cases having the disease for 1–6 months. The most common morphologic types of LP were classical LP 35 (57.4%), LP hypertrophicus 7 (11.5%), follicular LP 5 (8.2%), eruptive LP 3 (4.9%), and LP pigmentosus 2 (3.3%). Site of involvement was skin only in 34 (55.73%) cases, skin along with extra-cutaneous sites in 24 (39.9%) cases (oral: 10, nail: 7, oral+ nail: 7), and nail alone in 3 (4.9%) cases.

The clinical and demographic statistics of the study population are given in Table 2. The background characteristics of the cases and controls were comparable except for obesity, which was significantly higher in cases than controls ($P = 0.004$). LP cases showed significant association with hypertension ($P = 0.004$), IFG ($P = 0.025$), dyslipidemia ($P = 0.002$), MS ($P = 0.006$), and raised ESR ($P = 0.006$) [Table 2].

Among the lipid profile parameters, significantly higher values of TC ($P = 0.040$), TGs ($P = 0.013$), and

Table 2: Demographic and clinical characteristics of the study population (*n*=122)

Parameter	Lichen planus cases (*n*=61)	Controls (*n*=61)	*P*	OR (95% CI)
Age (Years), mean±SD	42.48±13.47	42.46±13.02	0.995	1.00 (-4.73-4.77)
Gender, M/F	36/25	36/25	1.00	1.00 (0.49-2.06)
Smoker, *n* (%)	11 (18)	14 (23)	0.501	0.74 (0.31-1.79)
Alcoholic, *n* (%)	10 (16.4)	5 (8.2)	0.168	2.20 (0.70-6.86)
Sedentary lifestyle, *n* (%)	13 (21.3)	10 (16.4)	0.487	1.38 (0.55-3.44)
Non-vegetarian diet, *n* (%)	50 (82.0)	48 (78.7)	0.649	1.23 (0.50-3.01)
Obesity (BMI), *n* (%)	23 (37.7)	9 (14.8)	0.004	3.50 (1.45-8.40)
Central obesity (WC), *n* (%)	27 (44.3)	11 (18)	0.002	3.61 (1.58-8.24)
Central obesity (WHR), *n* (%)	38 (62.3)	20 (32.8)	0.001	3.39 (1.61-7.13)
Central obesity (WHtR), *n* (%)	36 (59)	15 (24.6)	<0.001	4.2 (2.04-9.58)
Impaired fasting glucose, *n* (%)	14 (23)	5 (8.2)	0.025	3.34 (1.12-9.95)
Hypertension, *n* (%)	19 (31.1)	6 (9.8)	0.004	4.15 (1.52-11.29)
Dyslipidemia, *n* (%)	43 (70.5)	26 (42.6)	0.002	3.22 (1.52-6.80)
Metabolic syndrome, *n* (%)	18 (29.5)	6 (9.8)	0.006	3.83 (1.40-10.50)
Raised ESR, *n* (%)	41 (67.2)	26 (42.6)	0.006	2.76 (1.32-5.77)

OR: Odds ratio; CI: Confidence interval; SD: Standard deviation; M: Male; F: Female; BMI: Body mass index; WC: Waist circumference; WHR: Waist-to-hip ratio; WHtR: Waist-to-height ratio; ESR: Erythrocyte sedimentation rate

VLDL-C (P = 0.001) were observed in cases than the controls. There was no significant difference found in the lipoprotein ratios between the two groups. LP cases showed significantly higher values of anthropometric measurements, systolic and diastolic blood pressure, FBS, and ESR [Table 3]. Stratified analysis of CV risk factors in dyslipidemic study subjects revealed that younger LP patients (<50 years), males, non-obese, non-alcoholic, non-sedentary, normotensive, and patients with raised ESR were more associated with dyslipidemia as compared to control group [Table 4].

We compared the CVD risk factors in cases with MS (29.5%) and cases without MS (70.5%) and found comparable disease duration and age at enrollment but cases with MS showed significantly higher values of WC (P < 0.001), BMI (P < 0.001), WHR (P = 0.002), and WHtR (P < 0.001). In addition, cases with MS also showed higher values of TGs (P = 0.001), VLDL (P = 0.007), AIP (P < 0.001), and ESR (P < 0.001).

The CVD risk factor distribution according to extent of LP was also analyzed. We found a high proportion of dyslipidemia (83.3% vs. 64.7%) and MS (37.5% vs. 26.5%) in LP cases with skin and extracutaneous involvement as compared to LP cases with skin involvement only; however, the difference was not significant. In addition, LP cases with skin and extracutaneous involvement had a significantly longer duration of disease (P = 0.007) and higher values of TGs (P = 0.021) and ESR (P = 0.029).

Association between lipid levels and ESR was studied in cases of LP. ESR showed a significant negative correlation with HDL-C (P = 0.021, r = –0295). However, all other lipid parameters and ratios, except for TC, had a significant positive correlation with ESR [Figure 1]. We could not find any correlation between the duration of disease and ESR or any of the lipid parameters.

In a multivariate logistic regression analysis [Table 5], LP was found to be significantly associated with dyslipidemia (Adjusted OR 2.53, CI: 1.09–5.85; P = 0.030) and obesity (Adjusted OR 2.07, CI: 0.72–5.97; P = 0.032) even after adjusting for age, gender, sedentarism, dietary habits, IFG, and alcohol consumption. In another regression model with dyslipidemia as dependent variable (Model:

Table 3: Comparison of lipid profile parameters, anthropometric measurements, hemodynamic and metabolic parameters, and inflammatory markers between cases and controls (n=122)

Parameter	Lichen planus cases (n=61)	Controls (n=61)	P
Lipid profile (mg/dL)			
TC	183.57±44.50	168.52±35.15	**0.040**
TGs	145.00 (107-178)	126.00 (103-147)	**0.013**
HDL-C	47.00 (41-54)	46.0 (40-52)	0.654
LDL-C	117.46±32.02	111.43±20.37	0.217
VLDL-C	28.00 (23-35)	23.00 (18-29)	**0.001**
CR-I	3.96±1.26	3.67±1.09	0.176
CR-II	2.38 (1.91-3.20)	2.44 (2.06-2.80)	0.690
AIP	0.47±0.20	0.42±0.17	0.134
AC	2.96±1.26	2.67±1.09	0.176
Fasting blood sugar (mg/dL)			
FBS	88.00 (81-102.50)	83.00 (78-91)	**0.011**
Anthropometric measurements			
Height (cm)	164.18±9.05	165.89±8.00	0.272
Weight (Kg)	65.00 (55.50-74.50)	60.00 (55-66.50)	**0.049**
BMI (Kg/m^2)	24.03 (20.72-26.04)	22.35 (20.45-23.55)	**0.014**
WC (cm)	83.97±15.68	74.43±12.53	**<0.001**
HC (cm)	92.00 (85.50-99.50)	88.00 (79-94)	**0.001**
WHR	0.90 (0.87-0.96)	0.87 (0.79-0.91)	**0.005**
WHtR	0.51±0.10	0.45±0.08	**<0.001**
Hemodynamic parameters			
SBP	124.00 (120-132)	120.00 (110-24)	**<0.001**
DBP	80.00 (80-90)	80.00 (80-81)	**0.008**
Inflammatory markers (mm/h)			
ESR	18.00 (10-24.50)	10.00 (8-15)	**<0.001**

TC: Total cholesterol; TGs: Triglycerides; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; VLDL-C: Very-low-density lipoprotein cholesterol; CR-I: Castelli's risk index-I; CR-II: Castelli's risk index-II; AIP: Atherogenic index of plasma; AC: Atherogenic coefficient; FBS: Fasting blood sugar; BMI: Body mass index; WC: Waist circumference; HC: Hip circumference; WHR: Waist-to-hip ratio; WHtR: Waist-to-height ratio; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; ESR: Erythrocyte sedimentation rate; Significant associations are shown in bold face

Table 4: Stratification of cardiovascular risk factors in lichen planus cases and controls in the presence of dyslipidemia (*n*=122)

Variable (Subgroup)	*n*	Cases with dyslipidemia (*n*=61)	Controls with dyslipidemia (*n*=61)	OR (95% CI)	*P*
Total, *n* (%)	122	43 (70.5)	26 (42.6)	3.21 (1.52-6.80)	**0.002**
Age, *n* (%)					
<50 years	83 (68.03)	26 (63.4)	15 (35.7)	3.12 (1.27-7.64)	**0.012**
≥50 years	39 (31.97)	17 (85)	11 (57.9)	4.12 (0.89-19.0)	0.082
Gender, *n* (%)					
Female	50 (40.98)	18 (72)	14 (56.0)	2.02 (0.62-6.56)	0.239
Male	72 (59.02)	25 (69.4)	12 (33.3)	4.55 (1.69-12.25)	**0.002**
Lifestyle, *n* (%)					
Non-Sedentary	99 (81.15)	33 (68.8)	22 (43.1)	2.90 (1.27-6.61)	**0.010**
Sedentary	23 (18.85)	10 (76.9)	4 (40.0)	5.00 (.82-30.46)	0.102
Dietary habits, *n* (%)					
Non-Vegetarian	98 (80.33)	36 (72.0)	20 (41.7)	3.60 (1.55-8.36)	**0.002**
Vegetarian	24 (19.67)	7 (63.6)	6 (46.2)	2.04 (0.40-0.55)	0.392
Alcoholism, *n* (%)					
Non-alcoholic	107 (87.70)	34 (66.7)	22 (39.3)	3.09 (1.40-6.82)	**0.005**
Alcoholic	15 (12.29)	9 (90.0)	4 (80.0)	2.25 (0.11-45.72)	1.00
Impaired fasting glucose, *n* (%)					
Normal	103 (84.43)	29 (61.7)	24 (42.9)	2.15 (0.97-4.74)	0.057
Impaired	19 (15.57)	14 (100.0)	2 (40.0)	8.00 (2.19-29.25)	**0.003**
Obesity (BMI), *n* (%)					
Non-obese	90 (73.77)	24 (63.2)	20 (38.5)	2.74 (1.16-6.51)	**0.021**
Obese	32 (26.23)	19 (82.6)	6 (66.7)	2.38 (0.41-13.75)	0.370
Hypertension, *n* (%)					
Normotensive	97 (79.51)	27 (64.3)	21 (38.2)	2.91 (1.27-6.71)	**0.011**
Hypertensive	25 (20.49)	16 (84.2)	5 (83.3)	1.07 (0.09-12.69)	1.00
ESR, *n* (%)					
Normal	55 (45.08)	12 (60.0%)	17 (48.6%)	1.59 (0.52-4.84)	0.414
Raised	67 (54.91)	31 (75.6%)	9 (34.6%)	5.86 (1.99-17.20)	**0.001**

OR: Odds ratio; CI: Confidence interval; BMI: Body mass index; ESR: Erythrocyte sedimentation rate. Significant associations are shown in bold face; Significant associations are shown in bold face

Table 5: Multivariate analysis of association between lichen planus and cardiovascular risk factors (*n*=122)

Variable	OR	95% CI	*P*
Age (per year)	0.98	0.95-1.01	0.252
Sex (Male vs. Female)	1.25	0.46-3.42	0.662
Lifestyle (Sedentary vs. Non-sedentary)	1.07	0.35-3.22	0.908
IFG	2.26	0.69-7.47	0.180
Alcoholic	1.42	0.38-5.35	0.603
Obesity	2.86	1.09-7.50	**0.032**
Diet (Vegetarian vs. Non-Vegetarian)	1.10	0.37-3.23	0.865
Dyslipidemia	2.53	1.09-5.85	**0.030**

(Model: χ^2=18.71, *P*=0.016, –2 Log likelihood=150.413, Cox and Snell R^2=0.142, Nagelkerke R^2=0.190). OR: Odds ratio; CI: Confidence Interval; IFG: Impaired fasting glucose. Significant associations are shown in bold face

χ^2 = 29.950, *P* = 0.000, –2 Log likelihood = 137.073, Cox and Snell R^2 = 0.218, Nagelkerke R^2 = 0.292), besides gender, the presence of LP itself was one of the independent CVD risk factors for dyslipidemia (Adjusted OR 2.53, CI: 1.08–5.91, *P* = 0.033).

Discussion

The association between dermatological diseases and CVD risk is not new and dates back to over 100 years when for the first time in 1897, Strauss *et al.*[24] found the association of psoriasis with diabetes. Over the last few decades, research on this subject has gained momentum, and today literature is abundant with studies linking many dermatological diseases with an array of CVD risk factors.[7,8] Among all cutaneous disorders, psoriasis has the highest level of evidence to support its association with MS as well as its individual components.[8] In the present study, we found LP to be significantly associated with various CVD risk factors. The earliest report of LP having such an association came in 1974 and later in 1976, when LP was found to have an association with glucose intolerance and diabetes mellitus (DM).[25,26] Since then many studies have been conducted. A case report by Kurgansky *et al.*[27] in 1994 was the first in the literature to propose an association of LP with dyslipidemia. In 2009, a case-control study using an Israeli health database demonstrated LP to be

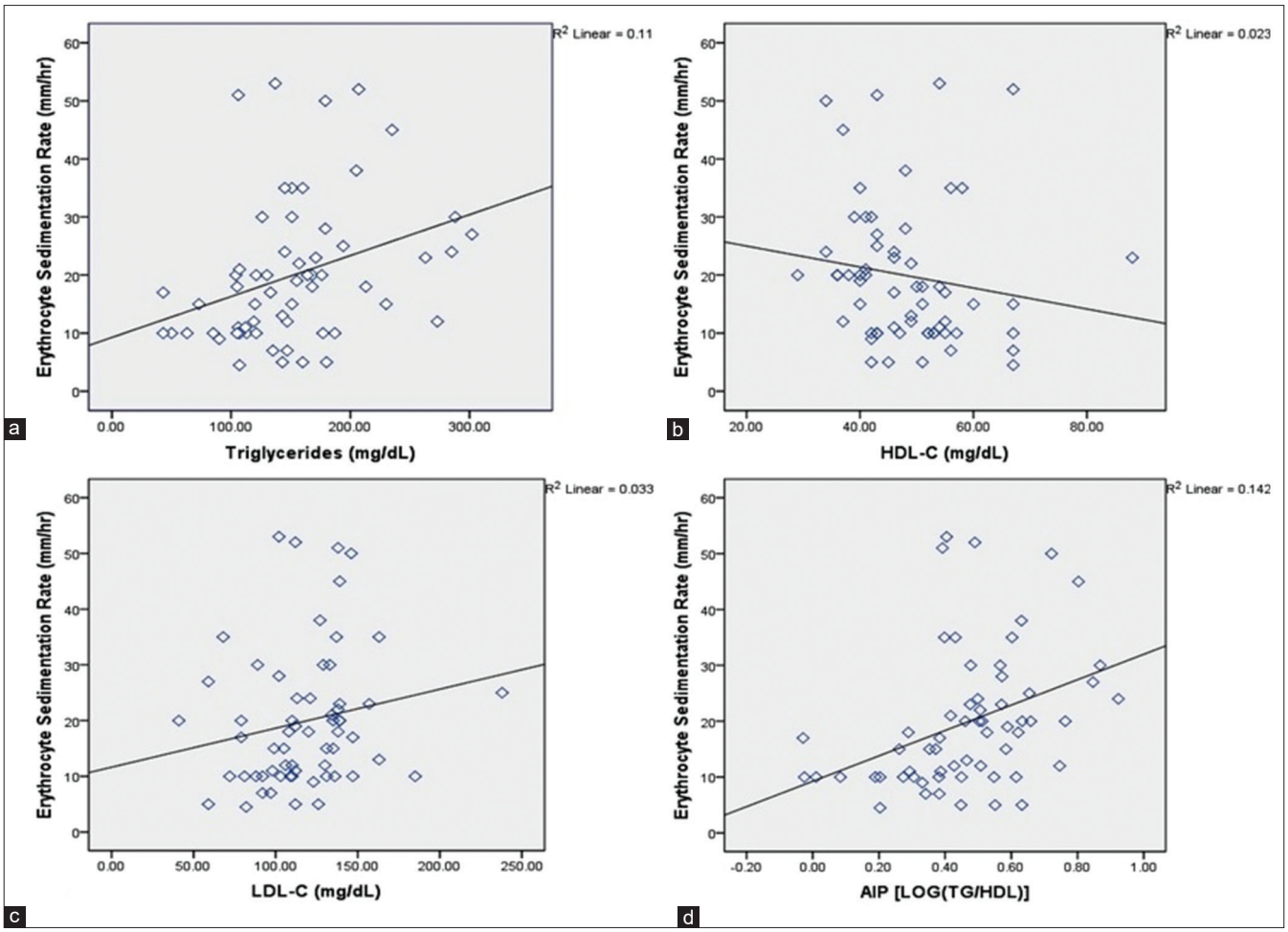

Figure 1: Correlation of ESR with lipid parameters and ratios. (a) Triglycerides (*r* = 0.418, *P* = 0.001); (b) High-density lipoprotein cholesterol (HDL-C) (*r* = –0.295, *P* = 0.021); (c) Low-density lipoprotein cholesterol (LDL-C) (*r* = 0.278, *P* = 0.030); (d) Atherogenic index of plasma (AIP) (*r* = 0.480, *P* < 0.001)

associated with dyslipidemia.[10] In subsequent studies, the association of LP with various CVD risks such as IFG, DM, deranged lipid parameters, obesity, MS, inflammatory markers, etc., have been studied. A comprehensive review of the literature of studies evaluating the association of CVD risk factors in LP is shown in Table 6.[5,10-17,25,26,28-32] Many of the studies exploring CVD risk factors associated with LP have focused on metabolic risk factors only and have not studied behavioral risk factors, which are known potential confounders [Table 6]. A recent meta-analysis has also established that LP is significantly associated with an increased risk of dyslipidemia.[7]

The present study found both total obesity and central obesity to be significantly higher in cases than controls. Central obesity is considered to be a better predictor of CVD risk than the total obesity and is usually assessed according to WC and WHR. However, recent evidence suggests WHtR to be a better marker of central obesity as cut-off values are not gender-specific.[21] In the present study, we also employed WHtR for assessing central obesity besides WC and WHR. This anthropometric parameter has not been employed in previous studies. Saleh *et al.*[13] found higher mean values of WC but the association with central obesity was not mentioned. In the study by Agarwala *et al.*,[15] central obesity was found to be significantly higher in LP cases than controls but Dreiher *et al.*,[10] Panchal *et al*.,[5] and Arias-Santiago *et al.*[11] found no association between LP and obesity.

Disturbances in glucose metabolism have been documented in many previous studies.[13,14,17] The present study also found significantly higher prevalence of IFG (23% vs. 8.2%, *P* = 0.025). Dreiher *et al***.**[10] and Arias-Santiago *et al*.,[11] however, found no association of LP with deranged blood sugar levels. Hypertension was found to be more prevalent in cases as compared to controls (31.1% vs. 9.8%, *P* = 0.004) unlike the findings of Baykal *et al.*[14] and Dreiher *et al.*[10] who found comparable distribution between cases and controls.

As per NCEP-ATP III criteria, a statistically significant difference was found in the distribution of dyslipidemia among cases and controls (70.5% vs. 42.6%, *P* = 0.002). These results are consistent with many previous studies,[5,10-13] but some studies have refuted the association of LP with dyslipidemia.[14,15] In our study, serum levels

Table 6: Review of literature of studies published on association of lichen planus and cardiovascular disease risk factors

Study	Year/Region	Study Design	Sample size/total LP cases	Major CV risk factors studied	Primary outcome measure/Significant association	Adjustment for confounders	Adjusted OR (95% CI) for Dyslipidemia/MS
Powell *et al*.[25]	1974/UK	Cross-sectional	21/21	GI	GI (55%)	ND	NA
Lowe *et al*.[26]	1976/UK	Cross-sectional	40/40	GI	GI (62%)	ND	NA
Seyhan *et al*.[28]	2007/Turkey	Case-control	60/30	IFG, DM, IR, OGTT	DM, IR, IFG	ND	NA
Dreiher *et al*.[10]	2009/Israel	Case-control (Retrospective)	4333/1477	Obesity, smoking, HTN, dyslipidemia, DM	Dyslipidemia	Age, gender, smoking, DM, HTN, SES, HT, obesity	**1.34 (1.14-1.57)**
Arias-Santiago *et al*.[11]	2011/Spain	Case-control (Retrospective)	200 (100)	Obesity, tobacco, FBS, HTN, dyslipidemia, MS, ESR, CRP, fibrinogen	Dyslipidemia, ESR, CRP, fibrinogen	Age, gender, BMI, FBS and CRP	**2.85 (1.33-5.09)**
Arias-Santiago *et al*.[12]	2011/Spain	Case-control	160/80	Obesity, smoking, alcohol, HTN, dyslipidemia, DM	Dyslipidemia	Age, gender, BMI, FBS	**3.03 (1.49-6.17)**
Atefi *et al*.[17]	2012/Iran	Cross-sectional	80/80	IFG, DM	DM	ND	NA
Saleh *et al*.[13]	2014/Egypt	Case-control	80/40	Obesity, dyslipidemia, DM, MS, hs-CRP, Hcy and fibrinogen levels	Obesity, dyslipidemia, DM, MS, hs-CRP, Hcy and fibrinogen levels	ND	NR
Polic *et al*.[29]	2014/Croatia	Case-control	102/72	Lipid levels	NS	ND	NA
Baykal *et al*.[14]	2015/Turkey	Case-control	158/79	Obesity, HTN, dyslipidemia, DM, IR, MS, ESR, CRP, fibrinogen	MS	ND	NR
Panchal *et al*.[5]	2015/India	Case-control	125/74	Obesity, FBS, dyslipidemia, CR-I, CRP, MDA, CAT.	Dyslipidemia, CR-I, CRP	Age, gender, CRP	NR
Aggarwala *et al*.[15]	2016/India	Case-control	117/39	Obesity, smoking, alcohol, tobacco, dyslipidemia, MS, ESR, CRP	MS, obesity	ND	NR
Yusuf *et al*.[30]	2015/Nigeria	Case-control	180/90	Obesity, HTN, dyslipidemia, DM	NS	ND	NA
Kar *et al*.[31]	2016/India	Case-control	80/40	Obesity, FBS and lipid levels	Higher mean lipid and glucose levels	ND	NR
Rashed *et al*.[32]	2017/Egypt	Case-control	230/110	MTHFR C677 gene polymorphism, Hcy, folic acid and lipid levels, HTN	MTHFR 677 genotype, Higher mean lipid and Hcy levels, decreased folic acid levels, HTN	ND	NR
Hashba *et al*.[16]	2018/India	Cross-sectional	70/70	Obesity, FBS, lipid levels, HTN, MS	NS	ND	NA
Present study	India	Case-control	122/61	Lifestyle, diet, smoking, alcohol, FBS, Obesity, HTN, dyslipidemia, DM, MS, ESR	Dyslipidemia, obesity, HTN, IFG, MS, ESR	Age, gender, lifestyle, alcohol, diet; IFG, obesity; smoker	Dyslipidemia: **2.53 (1.09-5.85)** MS: 3.93 **(1.33-11.62)**

OR: Odds ratio; CI: Confidence interval; ND: Not done; NR: Not reported; n=NA: Not applicable; NS: Not significant; GI: Glucose intolerance; IFG: Impaired fasting glucose; BMI; Body mass index; DM: Diabetes mellitus; IR: Insulin resistance; OGTT: Oral glucose tolerance test; HTN: Hypertension; HT: Hypothyroidism; SES; Socioeconomic status; Hcy: Homocysteine; MDA: Malondialdehyde; CAT: Catalase activity; CR-I: Castelli's risk index-I; TGs: Triglycerides; HDL-C: High-density lipoprotein cholesterol; MS: Metabolic syndrome; MTHFR: Methylene tetrahydrofolate reductase; CRP; C-Reactive Protein; ESR; Erythrocyte sedimentation rate. Significant association are shown in bold face

of TC, TGs, and VLDL-C were found to be significantly higher in cases than controls. Atherogenic indices (CR-I, CR-II, AIP, and AC), which are considered as predictors of atherosclerosis and CVD,[5] were also found to be higher in LP cases than controls, but the difference was not significant [Table 3]. Panchal *et al.*,[5] however, found significantly higher values of Castelli's risk indices (CR-I and CR = II) in LP cases.

MS, assessed using Harmonization criterion, was significantly more prevalent in cases as compared to controls (29.5% vs. 9.8%, $P = 0.006$). This is in concordance with the observations of Saleh *et al.*,[13] Baykal *et al.*,[14] and Aggarwala *et al.*[15] ESR levels were found to be significantly raised in cases as compared to controls ($P < 0.001$) consistent with Arias-Santiago *et al.*[11] who also studied other markers such as C-Reactive Protein (CRP) and fibrinogen. A significant positive correlation was found between ESR and serum levels of TGs, LDL-C, and VLDL-C and negative correlation with HDL-C.

We also assessed the CVD risk factors according to the extent of LP, hitherto not studied. Patients with skin and extracutaneous disease were found to have a longer duration of LP ($P = 0.007$) and higher values of TGs ($P = 0.021$) and ESR ($P = 0.029$). Although the prevalence of dyslipidemia and MS was also high in these cases as compared to patients with skin involvement alone, the difference was not significant. In addition, there was no significant association found between duration of LP and CVD risk factors. This may be because majority (66%) of the patients in our study had a short duration (<1 year) of disease. Association of CVD risk factors and morphologic type of LP could not be evaluated owing to the smaller number of patients in different types of LP. Furthermore, the multivariate models demonstrated a substantial association between LP and CVD risk factors after adjustment for potential confounders.

Stratification of CVD risk factors in LP cases and controls with dyslipidemia revealed that the association was more prominent among LP cases in the age group < 50 years, men, non-obese, non-alcoholic, non-sedentary, and normotensive patients. This is contrary to the usual norm where we expect subjects with dyslipidemia to be obese, alcoholic, sedentary, and hypertensive. The possible explanation is that LP, owing to its systemic inflammatory state may serve as an independent risk factor for dyslipidemia. This observation needs to be further evaluated and confirmed in additional studies.

We reviewed studies evaluating CVD risk factors in patients of LP and found paucity of studies conducted in the Indian population [Table 6]. There is considerable heterogeneity among these studies, and the overall results are inconsistent. Besides, all these studies are from Southern India, and none of these studies have adjusted for confounders.

The observations and results of the present study and the evidence gathered from a review of the literature supports the association of LP with CVD risk. The proposed explanation for such an association is inflammation, which is not only a key player in the pathogenesis of many dermatological diseases but is also at the core of understanding CVDs and risk factors. In LP, the inflammatory background created by the release of numerous cytokines such as TNF-α, IL-2, IL-6, IFN-γ, and TGF-β fuels up the systemic inflammation, which is known to produce metabolic derangements.[3]

Limitations

Our study being cross-sectional, temporal sequence cannot be established and association alone was proven and not causality. Further studies with larger sample size and longer follow-up period are needed to validate our results.

Conclusion

In the present study, of the various CV risk factors studied, total obesity, central obesity, impaired fasting glucose, hypertension, dyslipidemia, MS, and raised ESR were proportionally more in cases compared to controls. Chronic inflammation and acute phase reactants may be the underlying mechanism for such an association. Screening for the various CVD risk factors is therefore advisable, considering the long-term complications. It will be prudent to conduct follow-up studies to record CV events in LP patients. This may provide a better insight into the transition of the patients from having CVD risk factors to developing a CV event.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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