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The Association of Cutaneous Lichen Planus and Metabolic Syndrome: A Case-Control Study

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Abstract

Background: Previous research declares that metabolic syndrome (MS) is a cluster of risk factors that contribute to a significant level of incidence of cardiovascular diseases and diabetes mellitus. Lichen Planus (LP) is a potential factor to affect dyslipidemia and other components of MS.
Objectives: The aim of this research was to assess the association of MS, dyslipidemia, weight, hypertension, and diabetes mellitus with cutaneous LP.
Methods: To reach the goal of this research, a case-control study was designed. The study sample included 140 participants dividing into two groups of 70. The first group was selected from cutaneous LP patients while the second group was selected randomly. The groups were matched in terms of age and gender.
Results: The results of this research demonstrated that MS was present in 41 (58.6%) LP patients vs. 12 (17.1%) controls. (OR: 6.83; P value < 0.001). All metabolic syndrome criteria were significantly common among LP patients except for decreased high density of lipoprotein level. Dyslipidemia was observed in 57 (81.42%) patients vs. 25 (31.7%) controls (OR: 7.8; P value < 0.001). No statistically significant association was found between gender, the concomitant involvement of oral mucosa, hair, or nail and MS.
Conclusions: Based on the results of this research, it can be concluded that cutaneous LP is in association with a significant level of risk for metabolic syndrome, dyslipidemia, diabetes mellitus, and hypertension. It can also be concluded that the investigation of cardiovascular risk factors in these patients and focusing on the modification of their lifestyle and comorbidities are the other essential issues.

Keywords: Lichen Plan, Metabolic Syndrome

1. Background

Lichen planus (LP) is a chronic inflammatory disorder of the skin, hair, nail, and mucous membrane, affecting 0.2% - 5% of the population in the worlad (1). The affected cases are typically middle-aged individuals of both genders. The etiology of the disease remains obscure; however, LP is known to be a T-Cell Mediated autoimmune disease, resulting in Apoptotic damage of the Basal Keratinocytes expressing altered self-antigens on their surface (2).

The metabolic syndrome (MS) is a cluster of risk factors that contribute to a significant level of incidence of cardiovascular diseases and diabetes mellitus (3). It is estimated that around 20% - 25% of the world's adult population has MS and they are twice as likely to die from a cardiovascular complication in comparison with normal population (4).

Recent evidence suggests that the chronic inflammation, oxidative stress, and endocrine abnormalities, which are observed in dermatological diseases, have potentials to contribute to a higher level of risk for MS (5). Such association has been strongly observed with psoriasis (6, 7) and androgenetic alopecia (8), but it has been recently shown to extend to other skin diseases such as acanthosis nigricans, skin tags, hidradenitis suppurativa, systemic lupus erythematosus, chronic urticaria, and even skin cancers (5, 9).

Grinspan (1963) asserted that there is an association between oral LP and diabetes mellitus (DM) and hypertension (HTN), called "Grinspan's syndrome" (10). However, there is much research available that denies the above-mentioned association (11-13). Recent evidence suggests that LP can be

associated with dyslipidemia and other components of MS (14-21). The early investigation and diagnosis of MS in this population of patients will help control the risk factors and prevent the serious morbidity and mortality of cardiovascular events.

The goal of the current case-control study was to investigate the status of the metabolic parameters including weight, serum lipid profile, blood pressure, waist circumference, blood glucose levels, and the overall prevalence of MS in patients with LP as compared to control individuals.

2. Methods

This case-control study was performed by selecting 140 participants from Razi hospital located in Rasht, Iran, dividing into two groups. The first group encompassing 70 cases was selected from patients who suffered from cutaneous LP, while the second group encompassing 70 controls was selected randomly from healthy individuals. This study was approved by the ethics committee and institutional review board of Guilan University of Medical Sciences. The diagnosis of LP was made by expert dermatologists based on history and classic clinical presentation of cutaneous lesions and histopathological confirmation performed by a 4 mm punch biopsy in suspected cases (26 out of 70 patients). The inclusion criteria included participants who:1, had a minimum age of 18 years; 2, suffered from cutaneous LP; 3, received no previous or current treatment with immunosuppressive agents or systemic corticosteroids, and 4, accepted the offered informed consent. The following criteria were set to exclude the participants: 1, drug-induced lichen planus; 2, LP of hair, mucosal membrane, and nails without concomitant skin involvement. The control group was randomly selected from healthy participants with the following specifications: 1, presented to the given hospital at the cosmetic or plastic surgery centers; 2, having no history of inflammatory or autoimmune skin diseases, and 3, having the same age and gender. The following clinical data were collected: age, gender, weight (kg), height (m), waist circumference (WC) (cm), blood pressure (BP) (mmHg), and history of smoking. For all participants, body mass index (BMI) was calculated using Formula 1: Body mass index (BMI) calculation.

X: Weight (kg)

Y: Height (m)

Z: Body Mass Index (BMI)

Equation 1. Body Mass Index (BMI) Calculation

$$Z = \frac{X}{Y^2} \quad (1)$$

The WC was measured using the level of the most upper part of the hip bone without compression on the skin. Blood pressure was measured regarding a time criteria as further. Two samples were gathered, one after 10 minutes of rest in a sitting position and one after 15 minutes in the same position. Then, the mean of the two measurements was calculated and used. Fasting Blood Sugar (FBS), triglycerides (TG), total cholesterol (Chol), low-density lipoprotein (LDL-C), and high-density lipoprotein (HDL-C) were measured by using blood samples of 12 hours fasten participants, taken between 8 a.m. and 9 a.m. The process of data gathering had been started before the systematic treatments in order to avoid treatment-related dyslipidemia. According to the national cholesterol education program's ATP III criteria (4), MS was diagnosed if three or more of the following factors were present:

Table 1. Factors for Diagnosing MS

	Factors for Diagnosing MS
(i)	WC $\geq$ 102 cm (male), $\geq$ 88 cm (female)
(ii)	Plasma HDL-C < 40 mg/dL (male), < 50 mg/dL (female)
(iii)	hypertriglycidemia defined as plasma TG $\geq$ 150 mg/dL
(iv)	hypertension defined as BP $\geq$ 130/85 mmHg or use of medication for hypertension
(v)	hyperglycemia defined as FBS $\geq$ 110 mg/dL or use of medication for hyperglycemia

It should also be mentioned that according to the ATP III criteria (4), Dyslipidemia was diagnosed in presence of one of the following factors:

Table 2. Factors for Diagnosing Dyslipidemia

	Factors for Diagnosing Dyslipidemia
(i)	TG > 150 mg/dL
(ii)	Chol > 200 mg/dL
(iii)	LDL-C > 130 mg/dL
(iv)	HDL-C < 40 mg/dL

For statistical analysis, SPSS software (IBM, Version 22) was used.

The dataset was presented as frequencies and mean $\pm$ standard deviation (SD). Sample T-test, Chi-square test, and calculation of odds ratio (OR) were done when applicable. For evaluation, the P value level of 0.05 was selected and samples with P values lower than 0.05 were selected as statistically significant.

3. Results

The following specifications were observed in the participants: the mean age was 51.4 regarding an interval of

15.2; in terms of gender, 29 cases (41.4%) were male and 26 (37.1%) of the participants were smokers. It was also observed that all participants possessed classic cutaneous LP, with concomitant mucosal LP in 27 (38.6%), hair involvement in 8 (11.4%), and nail changes in 10 (14.3%) patients. No significant difference was observed between patients and control participants in terms of mean age, gender distribution, or frequency of smoking (Table 3).

The mean values of WC (95.8 $\pm$ 11.7 cm, P value $<$ 0.001), BMI (27.5 $\pm$ 3.4, P value $<$ 0.001), FBS (116.3 $\pm$ 35.5 mg/dL, P value $<$ 0.001), TG (179.3 $\pm$ 10.5 mg/dL, P value $<$ 0.001), and both systolic (131.6 $\pm$ 18.8 mm Hg, P value $<$ 0.001) and diastolic (82.9 $\pm$ 12.8 mmHg, P value $<$ 0.001) BP were significantly greater in LP patients than in the control group. The mean Chol (193.6 $\pm$ 42.8 mg/dL) and LDL-C (114.8 $\pm$ 39.5 mg/dL) were higher in patients than in controls but the difference was not statistically significant (Table 3).

The prevalence of each criterion of MS according to the ATP III definition in cases and controls is shown in Table 4. Significantly, a higher proportion of patients with LP had hypertension (47 (67.1%)), hyperglycemia (27 (38.6%)), hypertriglyceridemia (43 (61.4%)), and increased weight circumference (44 (62.9%)) in comparison with the control participants. (15 (21.4%), 9 (12.9%), 18 (25.7%), and 15 (21.4%), respectively). Overall, 41 (58.6%) of LP patients satisfied the criteria for MS in comparison with only 12 (17.1%) of the controls (P value $<$ 0.001, odds ratio (OR): 6.83). Dyslipidemia was presented in 57 (81.42%) of the patients in comparison with 25 (31.7%) controls and the difference was highly significant (OR: 7.8, P value $<$ 0.001). However, LP patients with MS had a higher level of BMI in comparison with those patients who had not the same issues. The results of the research showed no association between MS and gender or other cutaneous involvements such as oral mucosal, hair, or nail disease (Table 5).

4. Discussion

Previous research shows that MS affects approximately 15% - 25% of the general population of US and European adults (22, 23). Results of a systematic review (X, 2014) in Iran asserted that the prevalence of MS based on ATP III criteria was 27% (24). The MS is a factor that results in global epidemics of DM and cardiovascular diseases. Regarding the abovementioned facts, early identification of individuals with MS is effective and essential, since prescribing a set of lifestyle interventions or treatment help them prevent the occurrence or progress of diabetes and cardiovascular diseases as well as other complications such as the risk of stroke, fatty liver disorder, and even certain types of malignancies (25-27). Mortality risk after adjustment for conventional cardiovascular risk factors is around three times higher in patients with MS. 5Previous research studied the association of several dermatologic diseases with MS and its components. Although Psoriasis has consistently been associated with MS and its various components, currently this relationship is considered to extend to a wide spectrum of dermatologic diseases such as LP.

The goal of this research was to study the association of cutaneous LP with MS and its components. The results of this research showed that there was a significant level of prevalence of MS (58.6%) and dyslipidemia in Iranian patients with CLP and there was a strong association with all components of MS except for the HDL levels. Although there is a gap in the identification of the exact mechanism of the relationship between CLP and MS, it is assumed that the chronic inflammation is potent to link LP to the components of MS. The chronic inflammation is recognized to cause a persistent rise in the level of proinflammatory cytokines such as Leptin, Adiponectin, Tumor Necrosis Factor-α(TNF), Interleukin 6 (IL-6) and other Adipocytokines produced by Adipocytes (5, 28). LP is a chronic immune-mediated condition and possible Autoantigens are processed by Langerhans cells and then presented to T Lymphocytes.

The Lymphocytes attack Keratinocytes and during the Lymphocytotoxic process, an enhancement in the level of factors is observed: TNF-α, IL-6, IL-10, and IL-4 along with an upregulation in further factors CXCR3 ligands CXCL9, CXCL10, and CXCL11 by IFN-α (21). In addition, it should be considered that a disorder in the elimination of reactive oxygen species (ROS) can result in an increased level of circulating lipids and cholesterol in the blood which increases the risk of dyslipidemia and MS (29, 30). Based on the results of this research, an increased level of ROS and lipid peroxidation in LP was observed, which enhanced the inflammatory response by immunological mechanism and increased the serum level of nitric oxide, malondialdehyde, and superoxide dismutase (31-34).

Our findings showed that there was a significant level of MS risk among Iranian LP patients. In the same context, the results of the recent research by Baykal et al. (35) from Turkey and Saleh (19) et al. from Egypt confirm this issue. The prevalence of MS in various series (58.6%) in the current research was considerably higher than that in a previous study (26.6%), but this rate was lower than what was reported in the research of Saleh et al. (77.5%). LP cases showed increased prevalence in whole MS parameters of this study (FBS, WC, BP, and TG) except for decreased serum HDL. The findings are more consistent with those of Saleh et al. (19) study, while Baykal et al. (35) reported just increased mean levels of FBS and diastolic BP. In an earlier study, no increased prevalence of MS was found in Spanish patients with LP (21). While studies on the association of

Table 3. Comparison of Basic Characteristics and Mean Value ± Standard Deviation of Metabolic Parameters Among Lichen Planus Patients (n = 70) and Controls (n = 70)[a]

Variables	Patients	Controls	P Value
Sex			
Female	41 (59)	42 (60)	1
Male	29 (41)	28 (40)	
Smoking			
Yes	26 (37.1)	18 (25.7)	0.2
Age, y	51.4 ± 15.2	48.4 ± 14.9	0.24
BMI, kg/m^2	27.5 ± 4.3	24.1 ± 4.1	< 0.001
Waist circumference, cm	98.5 ± 11.7	86.7 ± 11.8	< 0.001
Systolic BP, mmHg	131.6 ± 18.8	117.7 ± 12	< 0.001
Diastolic BP, mmHg	82.9 ± 12.8	76.3 ± 9.4	0.0007
TG, mg/dL	179.3 ± 10.5	118.8 ± 6.9	< 0.001
Total cholesterol, mg/dL	193.6 ± 42.8	179.7 ± 44.2	0.06
LDL-C, mg/dL	114.8 ± 39.5	109.7 ± 40.5	0.45
HDL-C, mg/dL	44.2 ± 9.9	47.1 ± 9.6	0.08
FBS, mg/dL	116.3 ± 35.5	96.1 ± 16.2	< 0.001

Abbreviation: BMI, Body Mass Index; BP, Blood Pressure; TG, Triglycerides; LDL-C, Low Density Lipoprotein-Cholesterol; HDL, High Density Lipoprotein-Cholesterol; FBS, Fasting Blood Sugar.
[a]Values are expressed as No. (%).

Table 4. Comparison of Frequency and Odds Ratio of Metabolic Syndrome Indices, Diabetes Mellitus, and Frank Hypertension Among Patients with Lichen Planus and Control[a]

Variables	Patients	Controls	Odds ratio: CI 95%	P Value
MS	41 (58.6)	12 (17.1)	6.83: 3.12 - 14.94	< 0.001
MS Criteria				
Increased TG	43 (61.4)	18 (25.7)	4.6: 2.2 - 9.4	< 0.001
FBS ≥ 110 mg/dL	27 (38.6)	9 (12.9)	4.2: 1.8 - 9.9	0.0008
BP ≥ 130/85 mmHg	47 (67.1)	15 (21.4)	7.49: 3.5 - 15.9	< 0.001
increased WC	44 (62.9)	15 (21.4)	6.2: 2.9 - 13.1	< 0.001
decreased HDL	46 (65.7)	38 (54.3)	1.6: 0.8 - 3.1	0.168
Diabetes	15 (21.4)	3 (4.3)	6.09: 1.6 - 22.1	0.006
BP ≥ 140/90 mmHg	22 (31.4)	5 (7.1)	5.9: 2.1 - 16.8	0.0008
Dyslipidemia	57 (81.42)	25 (31.7)	7.8: 3.6 - 17.1	< 0.001

Abbreviations: BP, Blood Pressure; CI, Confidence Interval; FBS, Fasting Blood Sugar; TG, Triglycerides; HDL, High-Density Lipoprotein; WC, Waist Circumference.
[a]Values are expressed as No. (%).

MS with LP are limited, the observed heterogeneity can be explained by a variety of causes. First, genetic background, dietary habits, and levels of physical activity influence the frequency of MS and its components among different populations, making inter-population comparisons difficult. As stated earlier, the prevalence of MS in our LP population was more comparable to that of Egyptian series. Moreover, the selection criteria for cases and controls are crucially important and may seriously affect the observed results. This research solely considered patients with cutaneous LP, regardless of concomitant mucosal or hair/nail involvement, excluding drug-induced LP, exclusively mucosal LP, or patients receiving systemic treatments. We found that there is no association between genders, concomitant involvements of oral mucosa, hair, or nail with the prevalence of MS among LP patients. Baykal et al. (35) reported a higher

Table 5. Comparison of LP Patients with and Without Metabolic Syndrome[a]

Variables	LP Patients with MS	LP Patients Without MS	P Value
Sex			0.8
Female	28 (68.3)	13 (44.8)	
Male	13 (31.7)	16 (55.1)	
Extra cutaneous involvement			
Mucosal	19 (46.4)	8 (27.5)	0.13
Nail	5 (12.2)	5 (17.2)	0.7
Hair	3 (7.3)	5 (17.2)	0.26
BMI	29.25 ± 4.22	25.58 ± 3.47	< 0.001

Abbreviations: BMI, Body Mass Index; MS, Metabolic Syndrome.
[a]Values are expressed as No. (%).

level of prevalence of MS in mucosal than in cutaneous LP as well as in patients with longer disease duration. Other investigators have shown that there is an association between oral LP and oral lichenoid reaction and MS (20). It should also be mentioned that various clinical presentations of LP are in association with different risks of MS.

In this research, Dyslipidemia was significantly common in LP patients and we found a high level of prevalence of hypertriglyceridemia, hypercholesterolemia, increased serum LDL-C, and serum HDL-C levels that were lower than in control individuals but without a statistical significance. The association of LP and dyslipidemia has been documented in previous studies; Dr eiher et al.17 established this association in their case-control study based on a retrospective database review (42.5% vs. 37.8%). Arias-Santiago et al. reported a significant prevalence of serum lipid derangement in all parameters including TG, LDL-C, HDL-C, Chol, Total cholesterol/HDL-C, and LDL-C/HDL-C ratios among LP patients in comparison with controls (21). Oral LP and oral lichenoid reaction have also been associated with significant dyslipidemia (20). Other authors, however, did not find abnormal lipid levels in LP (18, 35). LP has long been associated with impaired carbohydrates metabolism and a higher prevalence of DM than in general population (10, 16, 36, 37). In accordance with our findings, multiple investigations supported co-association of LP with impaired glucose tolerance or DM (13, 14, 29, 38, 39). However, few studies did not mention any difference in glucose levels (21) or insulin resistance (35) in LP patients in comparison with controls. In addition to MS, which significantly increases the risk of cardiovascular events in LP patients, we found that there are additional risk factors such as higher BMI, increased prevalence of frank hypertension, and frank DM. Other researchers have reported higher levels of serum homocysteine, fibrinogen, and CRP in LP as risk factors for the hypercoagulable state, cardiovascular events, and atherosclerosis (19). Interestingly, electrocardiographic changes such as P-wave dispersion has been observed in LP patients as an independent risk factor for cardiac involvement and atrial fibrillation (4). The datasets of this research assert that the associated cardiovascular risk in LP may be considerable and should be looked for, prevented, and managed.

This study was limited to a narrow set of samples encompassing patients and controls. It also focused on cutaneous LP cases and the association of metabolic parameters with various LP clinical presentations, while other factors such as disease severity can also be studied. Therefore, in further research, it is expected that an expanded set of datasets be analyzed in order to define the correlation of MS with clinical subtypes and severity of LP.

4.1. Conclusion

We found a higher prevalence of MS, dyslipidemia, DM, and hypertension in patients with cutaneous LP. It is crucial to investigate the cardiovascular risk factors in these patients and focus on the modification of lifestyle and comorbidities.

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