Original Article

Comorbidities in Lichen Planus: A Case–control Study in Indian Patients

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Abstract

Background: Many previous studies have observed an association of lichen planus (LP) with one or two comorbidities such as diabetes mellitus and thyroid dysfunction. This study was undertaken to determine the association of LP with common comorbidities including diabetes mellitus, dyslipidemia, metabolic syndrome, thyroid dysfunction, and hepatitis C virus (HCV) infection. **Materials and Methods:** The study included 75 patients with clinical diagnosis of LP and 75 age- and sex-matched controls. After taking complete history, general examination and thorough dermatological examination were performed in all cases. Fasting serum samples were taken from all cases and controls and assayed for fasting plasma glucose, lipid profile, T3, T4, and thyroid-stimulating hormone levels, and anti-HCVantibodies. Metabolic syndrome was diagnosed according to 2005 revised National Cholesterol Education Programme's Adult Treatment Panel III. Two-sample Student's *t*-test was used for statistical analysis. **Results:** Increased triglyceride levels were seen in 26 cases (34.67%) compared with 14 controls (14%), which was significant ($P = 0.024$). Statistically significant increased prevalence of increasedlow-density lipoprotein levels ($P = 0.027$), low high-density lipoprotein levels ($P = 0.0189$), and diabetes mellitus ($P = 0.0217$) was also observed in LP. Metabolic syndrome ($P = 0.656$) and hypothyroidism ($P = 0.117$) were not significantly associated with LP. Strong association was observed between oral LP and hypothyroidism. All patients screened for anti-HCV antibodies were found to be negative. **Conclusion:** There is a clear associationof LP with dyslipidemia and diabetes mellitus. Screening for dyslipidemia and diabetes mellitus in all patients of LP will help in early detection, initiation of treatment, and prevent long-term morbidity.

Keywords: *Diabetes mellitus, dyslipidemia, lichen planus*

Introduction

Lichen planus (LP) is a common immune-mediatedpapulosquamous inflammatory skin disorder characterized clinically by flat-topped skin colored or violaceous pruritic papular eruptions.[1] The prevalence of LP was found to be between 0.22% and 1.2% of the adult population worldwide, depending on the geographic region studied.[2,3]

Common skin diseases such as psoriasis and androgenetic alopecia have been associated with lipid abnormalities and increased risk of cardiovascular disease.[4-7] LP is morphologically related to psoriasis and chronic inflammation in the skin is a hallmark of both these conditions. Recent studies have found an association of LP with abnormal carbohydrate metabolism, dyslipidemia, and hypothyroidism.[8-10] An epidemiological association of LP with hepatitis C virus (HCV) infection has also been reported in many European countries and Japan.[11,12]

Many previous studies have observed an association of LP with one or two of the above-mentioned comorbidities.[8-12] The objective of this study was to determine the association of LP with common comorbidities including diabetes mellitus, dyslipidemia, metabolic syndrome, thyroid dysfunction, and HCV infection in Indian patients.

Materials and Methods

This study was carried out in patients, who attended the outpatient department of dermatology, at a suburban medical college hospital. It was a prospective, hospital-based case–control study carried out over a period of 18 months from January 2015 to June 2016 after being approved by Institutional Ethics Committee. The sample size was calculated using difference of means formula. To achieve a power of study of 80% and precision (α) of 0.05 with a 95% confidence interval (CI), the estimated sample size per group was determined to be 75.

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In all, 75 clinically diagnosed LP cases of all ages and both sexes with a disease duration of at-least 3 months along with 75 age- and sex-matched controls were enrolled. The controls were patients with dermatoses other than LP, psoriasis, atopic dermatitis, and vitiligo attending the dermatology outpatient department. Patients who had more than one dermatologic disease, pregnant women, known patients of diabetes, hypertension, thyroid dysfunction, patients using hypolipidemic drugs, and patients who had received any systemic treatment for LP including oral corticosteroids, retinoids, methotrexate, and so on in thepast 6 months were excluded from the study.

After taking informed consent, general demographic data regarding age, sex, and contact information were noted. Detailed history was taken regarding duration of disease, progression of skin lesions, associated symptoms, history of treatment, and family history. General examination was performed and height, weight, and waist circumference were noted. Blood pressure was measured using manual mercury sphygmomanometer. Detailed dermatological examination was performed taking note of the extent, severity, and type of LP lesions. Skin biopsy for histopathological examination was done in all cases including cases with oral mucosal involvement to confirm diagnosis of LP.

Venous samples were taken from all patients and controls after an overnight fast of at least 8 h for measuring plasma fasting glucose and serum lipid levels. Plasma glucose levels were measured using glucose oxidase method, and serum triglycerides, high-density lipoproteins (HDLs), and low-density lipoproteins (LDLs) were measured with enzymatic procedures. Diagnosis of diabetes mellitus was made when fasting blood glucose was more than 126 mg/dL. Dyslipidemia was diagnosed if any one of the following parameters were abnormal: LDL more than 160 mg/dL or triglycerides more than 150 mg/dLor HDL less than 40 mg/dL in males and less than 50 mg/dL in females. For diagnosis of thyroid abnormalities, thyroid assay which included T3, T4, and thyroid-stimulating hormone (TSH) levels were measured. Thyroid hormones were assayed by radioimmunoassay (RIAK -5/5A, BARC). A diagnosis of hypothyroidism was made when thyroid function tests showed an increased TSH with or without low T_3/T_4 levels. Hyperthyroidism was diagnosed if T_3/T_4 levels were increased with associated lowered levels of TSH. Screening for HCV infection was done by detecting anti-HCV antibodies using enzyme-linked immunosorbent assay method.

Metabolic syndrome was diagnosed by the presence of three or more of the five criteria of 2005 revised National Cholesterol Education Programme's Adult Treatment Panel III (NCEP ATP III).[13] Numerical and graphical techniques were used to summarize and present the quantitative data collected from all patients and controls. Statistical analysis was done using two-sample Student's *t*-test to compare mean values of quantitative variables, and *P* value less than 0.05 was considered as statistically significant.

Results

In this study, 43 (57.33%) patients with LP were females compared with 32 (42.66%) males with a female-to-male ratio of 1.419:1. The majority of patients with LP belonged to the age group of 16–45 years (56.03%) and the mean age of presentation was 35.12 years [standard deviation (SD) = 8.03 years]. The duration of the disease was less than 2 years in 59 patients (78.67%), whereas disease duration of more than 2 years was seen in 16 patients (21.33%) with mean disease duration of 18.23 months (SD = 1.61 years). According to NCEP ATP III criteria, elevated waist circumference and elevated blood pressure were seen in 15 (20%) and 14 (18.66%) patients with, respectively.

The most common morphological types of LP observed in this study were as follows: classical LP in 25 cases (33.34%) followed by hypertrophic LP in 16 (21.33%) and oral LP in 12 cases (16%). Less common variants observed were generalized eruptive LP in 8 cases (10.66%), LP pigmentosus in 6 (8%), lichen planopilaris in 3 (4%), linear LP in 2 (2.67%), palmoplantar LP in 2 (2.67%), and actinic LP in 1 case (1.33%). Oral LP was seen in 12 patients (16%), of which reticular lacy pattern was the commonest subtype. Histopathological findings in all the 75 cases were consistent with LP.

In this study, increased triglyceride and LDL levels were seen in 26 (34.67%) and 11 (14.66%) cases, respectively compared with 14 (18.66%) and 3 (4%) controls, respectively, which was statistically significant *(P* = 0.024 and *P* = 0.027). Low HDL levels were observed in 36 cases (48%) and 22 controls (29.34%) which was statistically significant *(P* = 0.0189). Diabetes mellitus was diagnosed in 24 cases (32%), compared with 12 controls (16%) which was statistically significant *(P* = 0.021). The presence of both diabetes mellitus and dyslipidemia was detected in 20 cases of LP; the presence of diabetes and hypertension was seen in 9 cases, dyslipidemia and hypertension were noticed in 8 cases, and 5 cases had diabetes, dyslipidemia, and hypertension. The presence of both diabetes mellitus and dyslipidemia was not related to the duration of LP as it was present in 16 of 59 patients having LP for <2 years and 4 of 16 for ≥2 years *(P* = 0.221). Among patients with diabetes and dyslipidemia, classical LPwas seen in 8 cases, hypertrophic LP in 4 cases, oral LP in 3 cases, eruptive generalized LP in 2 cases, LP pigmentosus in 2 cases, and lichen planopilaris in 1 case. Metabolic syndrome, diagnosed as per NCEP ATP III criteria, was prevalent in 13 cases (34.67%) and 11controls (14%) which was statistically insignificant (*P* = 0.656) [Table 1].

Increased prevalence of hypothyroidism was noted in 8 cases (10.67%) and 3 controls (4%) which was

Table 1: Prevalence of dyslipidemia, diabetes mellitus, metabolic syndrome, and hypothyroidism in LP cases and controls

Lipid parameter/ other comorbidities	Cases	Controls	*P*
Elevated TGL	26 (34.67%)	14 (18.67%)	0.024
Elevated LDL	11 (14.66%)	3 (4%)	0.024
LowHDL	36 (48%)	22 (29.34%)	0.0189
Diabetes mellitus	24 (32%)	12 (16%)	0.0217
Metabolic syndrome	13 (17.34%)	11 (14.66%)	0.656
Hypothyroidism	8 (10.67%)	3 (4%)	0.117

TGL = Triglyceride; LDL = Low-density lipoprotein; HDL = High-density lipoprotein

statistically insignificant (P = 0.117). Hypothyroidism was observed in 4 males and 4 females (P = 0.263). However, hypothyroidism was relatively more common in cases of oral LP with a prevalence of 4 of 12 cases (33.33%) compared with the overall prevalence of 10.67% which was statistically significant (P = 0.005). All the patients found to have hypothyroidism had no other comorbidities such as diabetes, dyslipidemia, and hypertension. Hyperthyroidism was not detected in any of the cases and controls. In both cases and controls, no single subject was found to have anti-HCV antibodies.

Discussion

LP is an inflammatory papulosquamous disease affecting the skin, mucous membranes, and nails which may present with several morphological variants including the classic type, oral, hypertrophic, follicular, linear, actinic, and bullous LP. Although the precise etiology and pathogenesis of LP remain unclear, LP is considered to be an autoimmune process in which delayed hypersensitivity reaction leads to apoptosis of keratinocytes resulting in generation of free radicals and up-regulation of many cytokines and chemokines such as interleukin (IL)-2, IL-6, and interferon-α. Recent evidence suggests that various dermatological diseases including psoriasis and LP are associated with metabolic syndrome and its components.

Metabolic syndrome, first described by Gerald Reaven in 1988, is a cluster of risk factors including central obesity, atherogenic dyslipidemia, hypertension, and glucose intolerance.[14] It is a strong predictor of cardiovascular disease and confers cardiovascular risk higher than the individual components.[15] There have been many studies linking psoriasis to individual components of metabolic syndrome since 1950s.[4] In 1998, Petrou-Amerikanou *et al*. have reported significantly higher prevalence of diabetes mellitus (both types 1 and 2) in oral LP.[16] In 2012, Dreiher *et al*. observed an association of dyslipidemia with LP.[9] Since then, many other prospective studies have found positive evidence linking dyslipidemia and diabetes mellitus with LP.[16,17]

In this study, increased triglycerides were seen in 26 cases (34.67%) and 14 controls (18.67%) which was statistically significant (P = 0.024). Increased LDL levels and low HDL levels were also significantly more common in LPcases than controls (P = 0.027 and 0.0189, respectively). Similar results of hypertriglyceridemia, higher LDL levels, and low HDL levels in LP have been observed by Dreiher *et al*., Krishnamoorthy *et al*., and Panchal *et al*.[9,17,18] There was a statistically significant higher prevalence of diabetes mellitus in cases of LP (P = 0.021) which was in accordance with previous studies by Seyhan *et al*. and Atefi *et al*.[8,19] Higher prevalence of diabetes mellitus in cases of oral LP was noted by Petrou-Amerikanou *et al*. and Romero *et al*.[16,20] Several mechanisms have been suggested to explain the association of LP with dyslipidemia including chronic inflammation, increase in inflammatory markers such as CRP, and increased immunological activity of T-helper cells with the release of cytokines such as TNF-α and IL-6.[17] Diabetes mellitus and LP are characterized by autoimmune phenomenon and activation of T-cell immune responses, respectively, suggesting that common immunological trigger factors may play a critical role in the appearance of LP in diabetes mellitus.[21]

Clear association of LP with metabolic syndrome was not observed in this study (P = 0.656). Although a strong association of LP with metabolic syndrome has not been demonstrated in this study, significant prevalence of individual components of metabolic syndrome such as diabetes mellitus and low HDL confers increased cardiovascular risk in LP.

Hypothyroidism was detected in 8 cases (10.67%) and 3 controls (4%)(P = 0.117). Interestingly, of 12 cases of oral LP, 4 patients (33%) had hypothyroidism, which was statistically highly significant (P = 0.005). Siponen *et al*. and Romero *et al*. also observed a higher prevalence of hypothyroidism in oral LP.[10,20] In this study, none of the cases and controls had anti-HCV antibodies. Previous studies conducted in Italy, France, Japan, and Spain showed increased prevalence of anti-HCV antibodies in LP, but no Indian studies including ours corroborated this finding.[22-25]

To conclude, our study shows a clear association of LP with dyslipidemia and diabetes mellitus. Oral LP was strongly associated with hypothyroidism. No significant association of LP with metabolic syndrome and HCV infection could be established. These findings clearly establish that it is useful to screen for dyslipidemia and type II diabetes mellitus in all patients with LP. Patients with oral LP should also be screened for thyroid dysfunction. Prompt treatment in all detected cases will help in preventing long-term morbidity and complications.

Conclusion

Prevalence of dyslipidemia and diabetes mellitus were significantly associated with lichen planus. Oral lichen

planus was strongly associated with hypothyroidism. Association of metabolic syndrome and HCV with lichen planus could not be established.

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Conflicts of interest

There are no conflicts of interest.

References

1. Daoud MS, Pittelkow MR. Lichen planus. In: Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, Wolff K, editors. Fitzpatrick's Dermatology in General Medicine. 8th ed. New York: Mc Graw Hill; 2012. p. 296-312.
2. Rao R, Sacchidanand S. Lichen planus and lichenoid disorders. In: Sacchindanand S, Oberai C, Inamdar AC, editors. IADVL Text Book of Dermatology. 4th ed. Mumbai: Bhalani Publishing House; 2015. p. 1090-13.
3. Piguet V, Breathnach S, Le Cleach L. Lichen planus and lichenoid disorders. In: Griffiths C, Barker J, Bleiker T, Chalmers R, Creamer D, editors. Rook's Textbook of Dermatology. 9th ed. Oxford: Wiley-Blackwell; 2016. p. 37.1-.20.
4. Jon Love TJ, Qureshi AA, Karlson EW, Gelfand JM, Choi HK. Prevalence of the metabolic syndrome in psoriasis: Results from the national health and nutrition examination survey 2003–2006. Arch Dermatol 2011;147:419-24.
5. Milcic D, Janković S, Vesić S, Milinković M, Marinković J, Ćirković A, *et al*. Prevalence of metabolic syndrome in patients with psoriasis: Ahospital-based cross-sectional study. An Bras Dermatol 2017;92:46-51.
6. Arias-Santiago S, Gutiérrez-Salmerón MT, Buendía-Eisman A, Girón-Prieto MS, Naranjo-Sintes R.A comparative study of dyslipidaemia in men and woman with androgenic alopecia. Acta Derm Venereol 2010;90:485-7.
7. Banger HS, Malhotra SK, Singh S, Mahajan M. Is early onset androgenic alopecia a marker of metabolic syndrome and carotid artery atherosclerosis in young Indian male patients. Int J Trichology 2015;7:141-7.
8. Seyhan M, Ozcan H, Sahin I, Bayram N, Karincaoglu Y. High prevalence of glucose metabolism disturbance in patients with lichen planus. Diabetes Res Clin Pract 2007;77:198-202.
9. Dreiher J, Shapiro J, Cohen AD. Lichen planus and dyslipidemia: Acase-control study. Br J Dermatol 2009;161:626-9.
10. Siponen M, Huuskonen L, Läärä E, Salo T. Association of oral lichen planus with thyroid disease in a Finnish population: Aretrospective case-control study.Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2010;110:319-24.
11. Nagao Y, Myoken Y, Katayama K, Tanaka J, Yoshizawa H, Sata M. Epidemiological survey of oral lichen planus among HCV-infected inhabitants in a town in Hiroshima Prefecture in Japan from 2000 to 2003. Oncol Rep 2007;18:1177-81.
12. Carrozzo M, Gandolfo S, Carbone M, Colombatto P, Broccoletti R, Garzino-Demo P, *et al*. Hepatitis C virus infection in Italian patients with oral lichen planus: A prospective case-control study. J Oral Pathol Med 1996;25:527-33.
13. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285:2486-97.
14. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes 1988;37:1595-1607.
15. Rodríguez-Zúñiga MJM, García-Perdomo HA. Systematic review and meta-analysis of the association between psoriasis and metabolic syndrome. J Am Acad Dermatol 2017;77:657-66.
16. Petrou-Amerikanou C, Markopoulos AK, Belazi M, Karamitsos D, Papanayotou P. Prevalence of oral lichen planus in diabetes mellitus according to the type of diabetes. Oral Dis 1998;4:37-40.
17. Krishnamoorthy B, Suma GN, Mamatha NS, Sowbhagya MB, Garlapati K. Lipid profile and metabolic syndrome status in patients with oral lichen planus, oral lichenoid reaction and healthy individuals attending a dental college in northern India –A descriptive study. J Clin Diagn Res 2014;8:ZC92-5.
18. Panchal FH, Ray S, Munshi RP, Bhalerao SS, Nayak CS. Alterations in lipid metabolism and antioxidant status in lichen planus. Ind J Dermatol 2015;60:439-55.
19. Atefi N, Majedi M, Peyghambari S, Ghourchian S. Prevalence of diabetes mellitus and impaired fasting blood glucose in patients with Lichen Planus.Med J Islam Repub Iran 2012;26:22-6.
20. Romero MA, Seoane J, Varela-Centelles P, Diz-Dios P, Garcia-Pola MJ. Prevalence of diabetes mellitus amongst oral lichen planus patients. Clinical and pathological characteristics. Med Oral 2002;7:121-9.
21. Fayyazi A, Schweyer S, Soruri A, Duong LQ, Radzun HJ, Peters J, *et al*. T lymphocytes and altered keratinocytes express interferon-gamma and interleukin 6 in lichen planus. Arch Dermatol Res 1999;291:485-90.
22. Cribier B, Garnier C, Laustriat D, Heid E. Lichen planus and hepatitis C virus infection. An epidemiologic study. J Am Acad Dermatol 1994;31:1070-2.
23. Gotoh A, Hamada Y, Shiobara N, Kumagai K, Seto K, Horikawa T, *et al*. Skew in T cell receptor usage with polyclonal expansion in lesions of oral lichen planus without hepatitis C virus infection. Clin Exp Immunol 2008;154:192-201.
24. Das A, Das J, Majumdar G, Bhattacharya N, Neogi DK, Saha B. No association between seropositivity for Hepatitis C virusand lichen planus: A case control study. Ind J Dermatol Venereol Leprol 2006;72:198-200.
25. Prabhu S, Pavithran K, Sobhanadevi G. Lichen planus and hepatitis c virus (HCV) – Is there an association? A serological study of 65 cases. Indian J Dermatol Venereol Leprol 2002;68:273-4.