A correlation between oxidative stress and hypertriglyceridemia in lichen planus - A case control study

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Abstract
Introduction and Objective: Chronic inflammation & lipid peroxidation plays a pivotal role in the etiopathogenesis of cardiovascular risks in many clinical conditions. Whereas, Lichen planus (LP), is a chronic skin inflammatory disorder which disturbs lipid metabolism & increases the lipid peroxides. However, there are limited data about the correlation between oxidative stress & hypertriglyceridemia in LP, hence the study was undertaken to 1) Estimate the levels of TG (triglycerides) & MDA (malondialdehyde) levels & 2) to correlate between the MDA & TG levels in LP patients.

Materials and Methods: A case control study was done at KIMS hospital, Hubli, which included 50 LP patients and 50 healthy individuals. Serum levels of TG (GPO-PAP method) and MDA (TBA method) was done.

Result: Patients with LP presented higher significant TG values (182.93 vs. 113 mg/dl), MDA values (4.81 vs. 3.99 nmol/ml) vs. controls. Also, our study showed positive correlation between TAG & MDA levels which is statistically significant (0.012).

Interpretation and Conclusion: Thus, the present study showed increased levels of TG & MDA, indicating that hypertriglyceridemia & lipid peroxidation may have domino effect with each other due to chronic inflammation & thereby may increase the cardiovascular complications in LP patients.

Keywords: Atherosclerosis, Cardiovascular risks, Dyslipidemias, Chronic inflammation, Lichen planus, Oxidative stress.

Introduction
Atherosclerosis, is one of the precursor to many diseases like stroke, peripheral vascular disease & myocardial infarction which increases impermanence across the worldwide. Overall, the disease is mainly due to the chronic inflammation, which is promoted by lipid accumulation & increased reactive oxygen species (ROS). But many subclinical skin inflammatory diseases like atopic dermatitis, lichen planus undergo undiagnosed for cardiovascular risks where its etiopathogenesis remains baffled. Lichen planus (LP) is a cryptogenic inflammatory disorder which impinges mainly on skin, mucous membranes, nails, and hair. Chronic inflammation, altered lipid metabolism and oxidative stress are accountable for increased frequency. Psoriasis, another chronic inflammatory skin disorder which is alike LP in etiopathogenesis, due to dysregulated T-cell interactions there is over expression of pro-inflammatory cytokines that leads to the hyperproliferation of keratinocytes and activation of neutrophils in the epidermis which finally results in chronic T-cell activation, resulting in persistent cycle of inflammation.

Not only that, this persistent inflammation causes the disturbances in lipid metabolism like low levels of High Density Lipoproteins – Cholesterol (HDL-C) or high levels of triglycerides. Hypercholesterolemia & hypertriglyceridemia are contributing risk factors, that can act individually or together for the development of atherosclerosis.

Origin of cellular degeneration in LP is believed to be subepithelial infiltration of T-lymphocytes that contributes to cytokines production which in turn can stimulate production of ROS and cause oxidative damage to tissues.

Oxidative stress represents as lipid peroxidation in the cell membranes which alters the lipid rich membrane fluidity and their signalling efficiency, leading to inflammatory changes and to aberrant cell proliferation responses. MDA (Malondialdehyde), is one of the end products of polyunsaturated fatty acid peroxidation & commonly used as a biomarker for oxidative stress. It has been proposed that a derangement in the elimination of ROS through sebum results in an increased blood level of circulating lipids and cholesterol, thereby increasing the risk of dyslipidemia.

Thus, chronic inflammation, lipid disturbances and lipid peroxidation may form a vicious cycle in the etiopathogenesis of LP, hence the present study was done to know the levels of TG & MDA & to correlate between the oxidative stress & hypertriglyceridemia in LP patients.

Materials and Methods
Study Participants: This case-control study was done at KIMS, Hubli. Ethical clearance was obtained from the Institutional Ethical Clearance Committee. Convienent sampling method was done as exact prevalence was unknown.

The study group consists of 50 diagnosed LP patients from the Dermatology Department OPD and the 50 healthy controls. Both the cases and controls are interviewed to obtain relevant data after taking informed consent.

Inclusion Criteria:
Cases: 1) > 18 years of either sex. 2) Newly diagnosed LP patients. 3) LP patients who stopped therapy.
Control: 1) >18 years of either sex. 2) Healthy individuals (without any skin manifestations/inflammatory diseases/cardiovascular/hypothyroidism/DM/HTN)

Exclusion Criteria:
1) Lichenoid drug eruption 2) Receiving treatment for LP such as systemic corticosteroids, retinoic acid, methotrexate. Diagnosis was made based on clinical symptoms and confirmed by histopathological features. Data were also gathered on age, sex, habits like smoking, alcohol consumption & hypothyroidism, personal history of cardiovascular disease & whether the patients were on antihypertensive, cholesterol lowering drugs. Weight and height was taken, thereby body mass index (BMI) was measured by the formula: weight in kg/height in m². The dyslipidemia was considered if one of the following parameters were present: 1) Triglycerides >150mg/dl; 2) Total cholesterol > 200mg/dl; 3) LDL-C >130mg/dl; or 4) the patient received treatment for dyslipidemia. In our study we are measuring only levels.

Method of Collection of Sample: After relevant history taking and informed consent, 5 ml of fasting venous blood were collected, allowed blood to clot and serum was separated & analyzed for TG, MDA levels.

Measurement of Triglycerides: Triglycerides were estimated by the GPO-PAP (glycerol phosphate oxidase-phenol antiaminopyrine) method by using standard kits, ERBA diagnostics on the fully automated analyzer.

Measurement of Malondialdehyde: MDA was done by TBA (thiobarbituric acid) assay on spectrophotometer at 535nm

Statistical Analysis
The statistical analyses were performed with the IBM SPSS software version 20.0 Independent sample student t test was used to compare mean values of variables & expressed as mean±SD. Pearson’s correlation coefficient was used to measure the relationship between TG & MDA levels. P<0.05 was considered significant in all analyses.

Results
A total of 100 individuals was studied, 50 with LP and 50 healthy controls. Among 50 cases, 29 were males and 21 were females.

Table 1 shows higher mean of height, weight & BMI in cases than controls which is statistically highly significant at p<0.0001

| Table 1: Mean values of age, height, weight & BMI among cases & controls |
|-----------------------------------------------|
| **Parameters** | **Cases** | **Mean±SD** | **t value** | **Controls** | **Mean±SD** | **t value** |
| AGE (yrs.) | 46.58±15.04 | 21.89 | | 48±14.1 | 23.82 | 0.0001 |
| HEIGHT (cms) | 158.62±16.99 | 65.78 | | 161.24±7.56 | 150.74 | 0.0001 |
| WEIGHT (kgs) | 62.55±11.28 | 31.18 | | 59.97±8.32 | 50.95 | 0.0001 |
| BMI | 29.40±38.04 | 5.46 | | 23.07±2.89 | 56.3 | 0.0001 |

Values are expressed as mean ± SD

| Table 2: Descriptive statistics of cases |
|----------------------------------------|
| **Parameters** | **N** | **Minimum** | **Maximum** | **Mean ± sd** |
| Triglycerides (mg/dl) | 50 | 44 | 576 | 182.93±127.2 |
| MDA (nmol/ml) | 50 | 3.32 | 6.31 | 4.81±0.82 |

N- number of cases

| Table 3: Descriptive statistics of controls |
|------------------------------------------|
| **Parameters** | **N** | **Minimum** | **Maximum** | **Mean±SD** |
| TAG (mg/dl) | 50 | 43 | 210 | 113.52±43.0 |
| MDA(nmol/ml) | 50 | 3.13 | 5.22 | 3.99±0.55 |

N-number of controls

| Table 4: Comparison between serum levels (mean±SD) of TG & MDA in cases & controls. |
|-----------------------------------------------|
| **Parameters** | **Cases** | **Mean±SD** | ** ‘t’ value** | ** ‘p’ value** |
| TAG (mg/dl) | 182.93±127.2 | 18.63 | .0001 |
| MDA (nmol/ml) | 4.81±0.82 | 51.13 | .0001 |

It is observed from table 4, that patients showed higher mean TG and MDA levels than the controls which was highly significant (p<0.0001) by application of student’s t test.
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**Fig. 1: Comparison of MDA levels among cases & controls**

![Bar chart showing MDA levels among cases and controls](chart1)

**Fig. 2: Sector diagram showing distribution of cases as per their TG**

Most of the cases (50%) had Triglycerides ranging between 100-200mg/dl

**Fig. 3: Sector diagram showing distribution of cases as per their MDA**

(40%) of the cases had MDA levels ranging between 4-5 nmol/ml
Table 5: Pearson’s correlation between serum TG & MDA levels among cases

| Parameters | MDA Levels |
|------------|------------|
| r value    | p value    |
| TAG        | 0.3        | 0.012*     |

It is observed from the table that there is positive correlation between TG and MDA levels with r values of 0.3 respectively which is statistically significant (< 0.012).

**Fig. 4: Pearson’s correlation co-efficient between serum TG levels with MDA levels among cases**

**Discussion**

LP is an idiopathic chronic inflammatory skin disorder and its etiopathogenesis are clearly unknown. It is believed to be T-cell immune mediated, where it stimulates the many proinflammatory mediators like cytokines, interleukins etc in turn causes the alterations in the lipid metabolism like hypertriglyceridemia. Also, the local production of inflammatory mediators can stimulate the production of ROS which damages the cell membrane by lipid peroxidation and thereby causing the disequilibrium between the pro-oxidants and antioxidants.

Table 1, showed higher mean values of weight and BMI in lichen planus patients than the controls which was statistically highly significant p (<0.0001). Increased BMI is one of the contributing risk factor for cardiovascular disease. Present study showed higher mean values of about 29.4 which is in the range of overweight. Also, our present study showed higher triglycerides values among LP patients which is one of independent marker for dyslipidemia & may contribute to the progression of atherosclerosis. Study by Melita Vuksic Polic et al, showed strong connection between the imbalanced concentrations of one or more serum lipids like hypertriglyceridemia and the occurrence of LP. Another similar case-control study by Salvador Ariaset al, included 200 patients, showed higher mean values of TAG with a positive correlation with cytokines, CRP.

Psoriasis, an autoimmune disorder quite similar to LP in etiopathogenesis. Since it is a T-cell immune mediated disorder, attacks on keratinocytes leading to generation of ROS & releases pro-inflammatory cytokines like TNF-α, IL-6, IL-10, IL-4 which are linked to cause dyslipidemia. Several other studies by Zari Javidiet al, Mallbris L et al, Pietrazak A et al, Jochen Schmitt et al, Isabela Guimaraes Ribeiro Baeta et al have shown that psoriasis has been linked to dyslipidemia.

Present study also showed higher mean MDA levels in lichen planus patients (4.81±0.82 vs 3.99±0.55) which is highly significant (p<0.0001) and shows that oxidative stress may play a role in pathogenesis. In systematic review by Shovana et al found that there is increased levels of MDA in eight studies & have role in the pathophysiology of oral lichen planus.

Oxidative stress where there is an increase in free radicals, which damages the cell membrane of the cell and thereby altering the functions. Cellular degeneration in LP is thought to be the sub epithelial infiltration of T-lymphocytes, which promote the formation of cytokines. These cytokines stimulate the production of ROS and products of lipid peroxidation triggering apoptosis that is a hallmark feature of lichen planus. Also, our study showed positive correlation which was statistically significant between triglycerides & malondialdehyde LP patients. As levels of triglycerides increases, the levels of malondialdehyde were increased which shows hypertriglyceridemia & oxidative stress interrelate with each other in its etiopathogenesis.

**Conclusion**

Thus, our study emphasizes that chronic inflammation in LP act as vicious cycle between hypertriglyceridemia & oxidative stress, where these factors can accelerate the cardiovascular risks in these patients. By knowing that, these factors may have role in etiopathogenesis would be helpful in LP patients for routine screening of dyslipidemia & thereby reduce the risk & complications of cardiovascular disease later in life as an early intervention.
Conflict of Interest: None.

References
1. Rui-Li Yang, Yong-Hui Shi, Gang Hao, Wu Li, Guo-Wei Le. Increasing oxidative stress with progressive hyperlipidemia in Human. Relation between malondialdehyde and atherogenic index. J Clin Biochem Nutr 2018;43:154-158.
2. Shekhari S Halder, UdayKhopkar. Clinical features of Lichen Planus. In: UdayaKhopkar, AmeetValia editors. Lichen Planus. 1st edition. Jaypee Brothers Medical Publishers (P) Ltd; 2013.chap 3.p 15-43.
3. Musa Sahin, Serap Gunes Bilgili, Hakkisimsek, Serkan Akdag, Aytac Akyol, et al. Increased P-wave dispersion in patients with newly diagnosed lichen planus. CLINICS 2013:68(6):846-850.
4. Gottlieb AB, Chao C, Dann F. Psoriasis co-morbidities. J Dermatol Treat 2008;19:5-21.
5. Nickolof BJ, Nestle FO. Recent insights into the immunopathogenesis of psoriasis provide new therapeutic opportunities. J Clin Invest 2004;113:1664-1675.
6. D. G. Aly and R. S. Shahin. Oxidative stress in Lichen Planus. Acta Dermatoven APA 2010;19(1):3-11.
7. Aps Waled Abdias, Taghreed Fadhil Zaidan, Abduladheem Y. Abbood Al-Barrak. Assessment of serum and salivary malondialdehyde in patients with oral lichen planus. J Bang Coll Dent 2014;26(2):99-102.
8. V. P. Jayasekharan, R. Ramya, K. Rajkumar, T. Dinesh Kumar, G. Nandhini, S. Satish Kumar. Estimation of nitric oxide and malondialdehyde in serum and saliva of patients with oral lichen planus. SRM J Res Dent Sci 2014;5(4):230-236.
9. Haliwell B, Gutteridge JMC. Free radicals in biology and medicine. New York: Oxford University Press 2002;8:701-707.
10. Briganti S, Picardo M. Antioxidant activity, lipid peroxidation and skin diseases. What’s new? J Eur Acad Dermatol Venereal 2003;17:663–669.
11. Kasperska-Zajac A, Brzoza Z, Rogala B, Polaniak R, Birkner E. Antioxidant enzyme activity and malondialdehyde concentration in the plasma and erythrocytes of patients with urticaria induced by nonsteroidal anti-inflammatory drugs. J Investig Allergol Clin Immunol 2008;18(5):372–375.
12. Sander CS, Ali I, Dean D, Thiele JJ, Wojnarowksa F. Oxidative stress is implicated in the pathogenesis of lichen sclerosis. Br J Dermatol 2004;151:627–635.
13. Tanmay Padhi, Garima. Metabolic syndrome and skin: Psoriasis Beyond. Spotlight of Psoriasis. Indian J Dermatol 2013;58(4):299–305.
14. Salvador Mena, Angel Ortega, Jose M. Estrela. Oxidative stress in environmental induced carcinogenesis. Mutat Res 2009;674:36-44.
15. Melita Vukasini Poli, Maja Miskulin, Kresimir Solic, Vera Puzaric, Miroslav Sikora Bruno Atalik. Imbalanced concentrations of serum lipids and lichen planus. Coll Antropol 2014;38(2):595-599.
16. Salvador Arias-Santiago, Agustin Buendia-Eisman, Jose Aneiro-Fernandez, Maria Sierra Giron-Prieto, Maria Teresa Gutierrez-Salmeron, Valentín Garcia Mellado et al. Cardiovascular risk factors in patients with lichen planus. Am J Med 2011;124(6):543-548.
17. Zari Javidi, Naser Tayyebi, Yalda Nahidi. Serum lipids abnormalities and psoriasis. Indian J Dermatol 2007;52(2):89-92.
18. Mallbris L, Granath F, Hamsten A, Stahle M. Psoriasis is associated with lipid abnormalities at the onset of skin disease. J Am Acad Dermatol 2006;54(4):614-621.
19. Pietrzak A, Chodorowska G, Szepietowski J, Zalewska-Janowska A, Krasowska D, Hersogava J. Psoriasis and serum lipid abnormalities. Dermatol Ther 2010;23(2):160-173.
20. Jochen Schmitt, Ulf Maywald, Natalie M. Schmitt, Michael Meurer, Wilhelm Kirch. Cardiovascular comorbidity and cardiovascular risk factors in patients with chronic inflammatory skin disease: A case-control study utilising a population-based administrative database. IJPH 2008;5(3):187-193.
21. Isabela Guimaraes Ribero Baeta, Bernardo Gontijo, Flavia Vasques Bittencourt, Eugenio Marcos Andrade Goulart. Comorbidities and cardiovascular risk factors in patients with psoriasis. An Bras Dermatol 2014;89(5):735-44.
22. Falguni H Panchal, Somshukla Ray, Remuka P Munshi, Supriya S Bhajraroa, Chitra S Nayak. Alterations in Lipid Metabolism and Antioxidant Status in Lichen Planus. Indian J Dermatol 2015;60(5):439-444.
23. Shovna Shivani Mishra, T.N. Uma Maheswari. Evaluation of oxidative stress in oral lichen planus using malonaldehyde: A systematic review. J Dermatol Dermatol Surg 2014:1-6.

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