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Assessment of mitochondrial DNA content and oxidative stress biomarkers in cutaneous lichen planus

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Abstract

Cutaneous lichen planus (CLP) is a chronic immune-mediated inflammatory dermatosis in which oxidative stress and mitochondrial dysfunction are increasingly implicated, yet integrated biomarker evidence remains limited. Methods: In this cross-sectional pilot study, 30 histopathologically confirmed CLP patients and 30 age- and sex-matched healthy controls were enrolled. Relative mtDNA copy number and telomere length were measured using quantitative real-time PCR, while serum TOS was estimated by a colorimetric assay. CLP patients had a markedly reduced mtDNA content in comparison to controls (246.95±69.95 versus 289.40±73.60; p=0.026). The relative telomere length was significantly greater in the CLP group (16279.92±2363.58 vs 14677.06±2528.51; p=0.021). TOS levels were elevated in CLP patients (32.11±14.67 vs 16.59±7.06 µmol H_2O_2 equivalents/L; p<0.0001), indicating a substantially more oxidative stress. CLP is linked to mitochondrial DNA depletion, modified telomere dynamics, and significant oxidative stress. These results support the hypothesis that mitochondrial malfunction and oxidative imbalance are pivotal in CLP development. Therapeutic approaches aimed at oxidative stress and mitochondrial well-being may provide potential advantages. Further long-term studies are needed to better understand the cause-and-effect correlations and therapeutic consequences.

KEYWORDS: Lichen planus; Mitochondria; DNA content; Oxidative stress.

Introduction

Lichen planus (LP) is a chronic, immune mediated inflammatory disease of skin, mucous membranes, nails, and hair. It is clinically manifested in violaceous, polygonal, flat-topped papules and plaques, which become severely pruritic. Wickham striae- fine, reticulated, white streaks are also a diagnostic feature. Adults aged 30 to 60 years have the highest prevalence rates of LP, but it can also occur in any age group [2]. Having a world-wide prevalence between 0.22 and 1 percent, the disease is still a significant dermatology issue, especially when chronic or affecting the mucosal area where the disease can be persistent, painful and hard to treat [1, 3]. The etiopathogenesis of LP is not fully known despite being clinically recognized as a long history disease. According to the present scientific consensus, LP is an autoimmune disease that is caused by T-cells, and cytotoxic CD8+ T lymphocytes attack basal keratinocytes [3]. An abnormal immune response to genetically susceptible persons can be caused by environmental conditions, which are viral infections, specific medications, and chemical exposures, which cause antigenic changes in the surface of the keratinocytes [3]. The subsequent mechanism of damaging the

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basal keratinocytes involves perforin-granzyme substances, Fas-Fas ligand, and the adaptive release of pro-inflammatory T cells after they have been activated [4]. LP histopathologically presents with a lichenoid band-like infiltrate of lymphocytes, degeneration of basal cells, incontinence of pigment and irregular saw-tooth rete ridges, which are manifestations of interface chronic dermatitis [5].

The systemic implications of LP have been the subject of increased interest, particularly its involvement in the presence of the metabolic dysfunction. A number of studies indicate the prevalence of metabolic syndrome (MS) is more prevalent in patients with LP. MS includes central obesity, dyslipidemia, impaired glucose tolerance and hypertension, which are all associated with insulin resistance and low-grade chronic inflammation that is chronic [6]. Co-existence of LP and MS implies similarity in the pathogenic pathways that are associated with immune dysregulation, oxidative stress, and disturbed metabolic pathways [7]. This notwithstanding, the results have been found to be mixed across populations to emphasize the necessity of conducting additional mechanistic studies [7,8]. Oxidative stress (OS) has proven to be a crucial element of LP pathogenesis. OS is caused by antioxidants being overwhelmed by reactive oxygen species (ROS), which leads to lipid peroxidation, protein oxidation and damage to DNA [9,10]. Feedback in oral lichen planus (OLP) has continuously reported increased oxidative indicators and disorders in the antioxidant. ROS promote epithelial injury, increased antigen presentation, and activates T-cells, which enhances the continuation of chronic inflammation [11]. Nonetheless, the contribution of OS to cutaneous LP has not been studied in as much detail and the mechanistic utility of this aspect is yet to be explained. The most important intracellular source of ROS is mitochondria, which plays a central role in the interactions between oxidative damage and inflammation [10]. Mitochondrial DNA (mtDNA), which is proximate to electron transport chain and does not have any protective histones, is susceptible to oxidative damage to a great extent. Mitochondrial dysfunction caused by damage to mtDNA decreases ATP production, enhances the formation of ROS, and reinforced the vicious cycle of mitochondrial dysfunction and oxidative stress [12]. It has been demonstrated that a reduced content of mitochondrial DNA has been observed in metabolic syndrome, insulin resistance, obesity, and cardiovascular disease, which opens the possibility that mitochondrial dysfunction is a biological connection between LP and dysfunction in systemic metabolism [13]. Another critical biomarker that is linked with oxidative stress is telomere length (TL). Chromosomes have their ends blocked by telomeres, which are susceptible to shortening by ROS as a result of the high concentration of guanine [14]. Rapid telomere shortening indicates a lifetime oxidative and inflammatory damage and leads to cell senescence. Although reduced length of telomeres has been documented in a number of chronic inflammatory conditions, very little and sporadic information is available on functionality of telomeres in LP, particularly in cutaneous lesions [14,15].

Since the overlapping between mitochondrial dysfunction, oxidative stress, and metabolic alterations may exist, and there are few studies on such aspects in cutaneous LP, there remains a lot to learn. There is evidence in the literature of OLP to support a mitochondrial involvement, but there are no similar results available regarding cutaneous LP. Furthermore, none of the former studies have measured the type of content of the mitochondrial DNA, the length of telomere as well as the systemic burden of oxidative in a perioperative manner and their relationship with metabolic variables have been studied in the context of the correlation coefficient. The current research was done to fill these gaps by considering the contents of the mitochondrial DNA, and oxidative stress indicators of telomere length and total oxidant status (TOS) in patients taking the cutaneous LP against the healthy ones. This investigation could help to elucidate the molecular pathways of LP and develop the information on the contribution of oxidative stress and mitochondrial dysfunction in the pathogenesis of this condition by combining these multidimensional biomarkers.

Materials and Methods

Design and Setting Study: This was a cross-sectional study done between April and August 2025 in the Department of Biochemistry and Dermatology, University College of Medical Sciences (UCMS) and Guru Teg Bahadur (GTB) Hospital, Department of Biochemistry and Dermatology, Delhi.

Ethical Approval: The protocol of the study was accepted by the Institutional Ethics Committee. All the participants received informed consent in writing before the study was carried out, and the study was conducted in compliance with the Declaration of Helsinki. The study ensured the strictness of participant confidentiality.

Sample Size Justification: The quantification of the mitochondrial DNA content, telomere length, and the overall oxidative state in the cutaneous lichen planus have not been previously performed, and it was not possible to conduct a formal calculation of the sample size. The research was

thus intended to be a pilot study. Depending on feasibility, preset period of time in which the study will take place and availability resources, 30 cases and 30 control age and sex matches were sampled to provide preliminary statistics to be used in future hypothesis-driven studies.

Population of the Study: Sixty participants were taken in and divided as follows: assured: Thirty patients with clinically diagnosed, histopathologically confirmed lichen planus. Controls Cross-sectional controls Thirty age- and sex-matched patients recruited into family of the patient. Eligibility Criteria: Inclusion Criteria: Adults of an age of 18 years and older, and lichen planus (case group) and apparently healthy subjects (control group), diagnosed via histopathy.

Exclusion Criteria: The patient with the following was not to include the study: Other dermatological disorders (e.g., psoriasis, systemic lupus erythematosus), pregnant or lactating, cardiovascular disease or stroke, scute febrile disease or active infection, Chronic systemic illnesses (e.g., autoimmune diseases, thyroid disease, peripheral vascular disease), antidiabetic or lipid lowering medication use and smoking, alcohol and intravenous drug use.

Sample Collection and DNA Extraction: under aseptic conditions, peripheral venous bloods were collected and DNA extracted. DNA extraction was done using two hundred microliters (200 µL) of anticoagulated –80 o C whole blood EDTA. All the genomic DNA was stored at -20C until the day of analysis as per the instructions of the manufacturer using the QIA amp DNA Blood Mini Kit (Qiagen, Germany) [16].

Outcome Measures: Relative mitochondrial DNA (mtDNA) content, oxidative stress biomarkers, such as Total Oxidative Status (TOS) and Relative telomere length.

Measurement of Mitochondrial DNA Content [16]: Quantification of relative copy number of the mitDNA was done by real-time polymerase chain reaction (qPCR) using the dye-based Chemistry on CFX Real-Time PCR System (Bio-Rad, USA) [17]. Mitochondrial and nuclear primers were employed and ratios of relative contents of the mitochondrial and nuclear DNA were calculated using cycle threshold (Ct) values, which are the copy number of the mitochondria, as compared to the nucleus.

Total Oxidative Status: Serum Total Oxidative Status measured through commercial colorimetric assay kit (Elabscience, USA) because of the protocol of the manufacturer [18]. Findings were given in terms of hydrogen peroxide equivalents, which are systemic oxidant load.

Telomere Length-Measurement: The relative telomere length was also calculated using real-time PCR, whereby telomeric repeats were amplified and the amplification normalized to a reference gene of one copy. Findings were in the form of telomere to single copy gene ratio [19].

Data Handling and Quality Control: All data were put in standardized case record forms and inputted in Microsoft Excel. There was cross-checking on data entry. To reduce the analytical variability, the standardized protocols lab tests were conducted upon the same conditions. The samples that have partial or irregular data were not included in the ultimate analysis.

Statistical Test: Continuous were given as mean and standard deviation (SD). Independent-samples t-test was used in comparing variables that were normally distributed and the Mann–Whitney U test in variables that were not normally distributed. The p-value of less than 0.05 was taken as significant.

Results

The study involved 60 participants (30 patients with histopathologically confirmed cutaneous lichen planus (CLP) and 30 age and sex matched control subjects). There were no gross differences between genders and those in the two groups were 46.7% males and 53.3% females respectively in both groups (n = 14 and 16 respectively).

Table1. Mitochondrial DNA (mtDNA) Copy Number in Cases and Controls

	Case (mean ± sd)	Control (mean±sd)	p-value
mtDNA content	246.95± 69.95	289.40±73.60	0.026*
Telomere-to-Single Copy Gene ratio	16279.92± 2363.58	14677.06± 2528.51	0.021*
TOS (µmol H_2O_2 equiv./L)	32.11± 14.67	16.59±7.06	<0.0001*

*Independent t-test**

The primary results were aimed at the content of mitochondrial DNA (mtDNA), relative telomere length (T/S ratio), as well as total oxidative status (TOS). It was statistically found that the content of the mitDNA was reduced significantly in CLP patients relative to the healthy controls. The average number of copies of the mtDNA in cases was 246.95 ± 69.95 and in controls the mean number of copies is 289.40 ±73.60 (p = 0.026). This observation indicates that the mitochondrial

abundance or integrity will be reduced in patients with CLP. Relative telomere length expressed as a ratio of telomere to single copy gene, T/S, was found to be significantly higher among the CLP patients (16279.92 ± 2363.58) than among the controls (14677.06 ± 2528.51; p = 0.021) (Table 1). Such a change suggests that telomeres are not regulated in CLP, which can be compensatory telomerase inactivation or altered cellular turnover caused by chronic inflammation and oxidative stress. A significant difference in the total oxidative status (TOS) was found in the two groups. The levels of TOS were significantly higher (32.11 ± 14.67 umol H2O2 equivalents/L) in patients with CLP in as compared with the controls (16.59 ± 7.06 umol H2O2 equivalents/L), which was of great statistical significance (p < 0.0001). This observation substantiates the existence of a concentration of a significantly greater systemic oxidative load in CLP patients. Altogether, these findings prove that cutaneous lichen planus is linked to substantial mitochondrial deficiency, impaired telomere biology, and increased oxidative stress even in the case of no overt metabolic abnormality.

Discussion

The current paper offers strong arguments to prove that the role of mitochondrial dysfunction and oxidative stress is an inherent aspect of cutaneous lichen planus pathology. The most significant observations are marked decrease of the content of the mtDNA and a sharp increase of the overall oxidative status as well as the change in the dynamics of telomere length in patients of CLP versus controls. The decrease in the level of the content of the mitochondrial DNA seems to indicate a disruption in mitochondrial biogenesis or an excessive damage of mitochondrion in CLP [20]. Mitochondria play a key role in controlling cellular energy metabolism and redox homeostasis, and oxidative damage to mtDNA is especially dangerous because it is located close to the electron transport chain and not covered by histones [20,21]. The same decline in the number of copies of the mitochondrial genetic material, has been described in chronic inflammatory, metabolic diseases like metabolic syndrome, insulin resistance, heart disease and cardiovascular disease, and serves as a motivation in favor of the hypothesis that mitochondrial dysfunction can be a common pathogenic process in inflammatory diseases [22,23]. Even though it was shown that mitochondrial participation exists in oral lichen planus in past, there has been little evidence regarding that of cutaneous LP before the current study, which builds on the idea to apply the concept to cutaneous disease [24]. The high level of TOS could be found in CLP patients which is a good evidence of systemic oxidative stress. Oxidative stress has been the subject of extensive implication in the pathogenesis of LP especially the oral LP where augmented lipid peroxidation items and lost antioxidant protections have been systematically recorded [24]. Reactive oxygen species have direct effects on keratinocytes, which include the heightened antigen presentation and the amplification of cytotoxic T-cell-mediated immunity, which continue to feed the chronic inflammatory cycle associated with LP [25]. This significant increased amount of TOS as found in the present study highlights the significance of oxidative imbalance as well in cutaneous LP. The present study made an interesting discovery that the relative telomere length significantly increased among CLP patients. Telomere contraction has typically been taken as one of the end results of long-term oxidative stress and cellular senescence, but paradoxical telomere overextension was reported in some diseases involving inflammation and autoimmune responses [26]. This phenomenon can be indicative of compensatory telomerase activation, or selective survival of immune cell subsets with longer telomes, or an enhanced proliferation of cells in categories stimulated chronically by the immune system [27]. These changes and their associated telomere dynamics have been seen in other inflammatory dermatoses and autoimmune conditions and point to telomere length changes in LP could be a multifaceted adaptive process and not mere erosion. Notably, the concomitants of low contents of mitDNA and increased oxidative stress levels indicate an autoinflammatory mechanism of gradual deterioration of mitochondrial maladaptation by oxidative damage in CLP patients. Overproduction of ROS destroys mitDNA, which subsequently causes mitochondrial dysfunction with the negative effect of promoting further ROS production to perpetuate inflammation [24]. This cycle could be very important in the disease chronicity in LP.

Conclusion

Clinical and mechanistic implications of the results of the current study are significant. They indicate that treatment models that attack oxidative stress and impaired mitochondrial performance including antioxidant supplementation or the administration of drugs that promote mitochondrial biogenesis could be of potential interest as ancillary therapy in LP. Nevertheless, to prove the causality or determine the effect of duration and extent of disease on these biomarkers, larger longitudinal studies are needed.

Conflict of interest: None

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