New markers of oxidative stress in lichen planus and the influence of hepatitis C virus infection – a pilot study

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Introduction. Lichen planus (LP) is a mucocutaneous T-cell mediated disorder of unknown etiology. There is growing evidence that oxidative stress is an important player in the pathogenesis of LP. Therefore, we have investigated oxidative stress markers in LP and the influence of hepatitis C virus (HCV) infection, a frequently associated condition, on oxidative stress in LP patients.

Method. We have determined the serum levels of 4- hydroxynonenal (4-HNE) and symmetric dimethylarginine (SDMA), as markers of oxidative stress, and total antioxidant capacity (TAC), as a marker of the antioxidant defence, in 4 groups: group A – HCV positive patients with LP (n=12), group B – HCV positive patients without LP (n=12), group C – HCV negative patients with LP (n=31) and group D – control group (n=26).

Results. In LP patients, we have identified an increased level of lipid peroxidation (4-HNE – group A – 8.41 ± 1.11 µg/mL, group B – 7.97 ± 2.17 µg/mL, group C – 7.81 ± 1.96 µg/mL and group D – 6.15 ± 1.17 µg/mL) and alterations in arginine methylation (SDMA – group A – 1.10 ± 0.24 µmol/L, group B – 1.03 ± 0.16 µmol/L, group C – 0.84 ± 0.19 µmol/L and group D – 0.50 ± 0.06 µmol/L) associated with a diminished antioxidant defence (TAC – group A – 234.50 ± 49.96 µmol/L group B – 255.83 ± 41.41 µmol/L, group C – 269.83 ± 43.33 µmol/L and group D – 316.46 ± 29.33 µmol/L), processes augmented by the association with HCV infection.

Conclusion. There is an imbalance between oxidants and antioxidants in patients with LP, an imbalance that is augmented by the presence of HCV infection. SDMA could be regarded as a novel biomarker of oxidative stress among these patients. To the best of our knowledge this is the first study to investigate the influence of HCV infection on oxidative stress in LP patients.

Key words: oxidative stress, 4-HNE, SDMA, lipid peroxidation, TAC, lichen planus, HCV infection.

What is new? What is important?

Studies regarding the influence of HCV infection on the redox status of patients with LP are not available in the medical literature. We have found higher serum levels of 4-HNE and SDMA as well as lower serum levels of TAC in LP patients and in those with LP and HCV infection when compared to controls. In addition, we have observed higher levels of 4-HNE and SDMA in association with lower levels of TAC in LP patients with HCV infection than in those without HCV infection. Moreover, both LP and HCV infection are characterized by an imbalance between oxidants and antioxidants. These data show that oxidative stress plays a role in LP pathogenesis and the process is amplified by HCV infection. Our study suggests that SDMA could be a reliable marker of oxidative stress in these patients.

INTRODUCTION

Oxidative stress defines the alteration of the balance between prooxidants and antioxidants, in favor of prooxidants. The main reactive oxygen species (ROS) include hydroxyl radical, superoxide anion and hydrogen peroxide. The hydroxyl radical is the most potent oxidant compound described so

far [1]. In the human body, free radicals are generated in various reactions such as the reduction of molecular oxygen during aerobic respiration, oxidation of catecholamines, etc. [1]. ROS play a dual role. ROS act as second messengers in various signaling pathways, are involved in the defence against infectious agents, modulate cell differentiation, regulate the expression of

proinflammatory cytokines, etc. [2]. When ROS accumulate in tissues exert a harmful effect, altering various tissue targets, the most frequently affected being lipids, proteins and nucleic acids. Antioxidants are molecules that interact with ROS, leading to their neutralization and thus protecting cells from their toxic effects [3]. Total antioxidant capacity (TAC) of the serum is a biomarker that reflects the antioxidant defence of the body [4].

Lichen planus (LP) is a chronic inflammatory disease of incompletely elucidated etiology, which affects the skin and mucous membranes. Regarding its pathogenesis, most researchers attribute great importance to T lymphocytes, considering LP a T-cell mediated autoimmune disorder, induced by exogenous or endogenous stimuli [5–7]. Several infectious agents have been suggested to play a role in the pathogenesis of LP. Most studies emphasize the association between hepatitis C virus (HCV) and LP. It has been shown that HCV can replicate in the oral mucosa leading to the activation of T lymphocytes, key players in the pathogenesis of LP [8]. The virus was detected in the saliva of the infected patients. These findings support the hypothesis that HCV infection can induce a cytotoxic reaction and the development of an autoimmune process [9–11]. It seems that a molecular mimicry might be involved, as keratinocytes are thought to display epitopes with similar structure to viral components [12].

Recent studies have revealed the involvement of oxidative stress in the pathogenesis of LP [13, 14]. It is also well known that in HCV infection the balance between oxidants and antioxidants is altered [15]. Polyunsaturated fatty acids (PUFAs), important components of membrane phospholipids, are the major target of oxidative stress. The skin includes a high amount of PUFAs in the cell membranes and an increased level of iron which both amplify the oxidative stress [16, 17]. The oxidative attack against PUFAs leads to the formation of a wide range of metabolites such as ethanal, propanal, hexanal, acrolein, glyoxal, malondialdehyde and 4-hydroxynonenal (4-HNE) [18].

4-HNE is derived from both endogenous and exogenous sources. Several mechanisms for the synthesis of lipoperoxides *in vivo* have been suggested, including enzymatic oxidation, non-enzymatic oxidation independent ROS and non-enzymatic oxidation mediated by ROS [16]. Several studies have established the mechanism of 4-HNE synthesis, its metabolic pathways,

reactivity, biological effects and pathophysiological role [19].

Lipid peroxidation has been previously studied in LP, especially in oral LP, being investigated other lipid peroxidation markers, especially MDA [20]. The study of 4-HNE could offer new insights in the pathogenesis of LP.

Post-translational modifications of proteins represent important events that occur under oxidative stress conditions [21]. Symmetric dimethylarginine (SDMA) and asymmetric methylarginine (ADMA) are amino acids that are generated intracellularly by post-translational modifications of arginine. ADMA is considered the most important inhibitor of nitric oxide synthase (NOS) [22]. SDMA does not directly affect the function of NOS but inhibits NO synthesis by arginine deficiency. SDMA has not been previously studied in patients with LP. Thus, investigating SDMA in patients with LP could highlight the role of post-translational modifications in proteins in this disorder.

The aim of our study was to investigate and identify new markers of oxidative stress in LP patients and assess the influence of HCV infection, a frequently associated condition, on oxidative stress in LP patients.

MATERIALS AND METHODS

We have conducted an observational study to determine the involvement of oxidative stress in the pathogenesis of LP, investigating the serum levels of 4-HNE, SDMA and TAC. Considering the association between LP and HCV infection, we have also investigated these markers in patients with LP and HCV infection in order to observe the influence of HCV.

This study was conducted between 2017 and 2019, in Victor Babes Infectious and Tropical Diseases Hospital. We included consecutive patients presenting to the hospital as follows, group A – HCV positive patients with LP (n=12), group B – HCV positive patients without LP (n=12), group C – HCV negative patients with LP (n=31) and group D – control group (n=26). In the control group we included healthy subjects, who addressed the dermatology clinic for disorders that do not interfere with oxidative stress markers such as skin tags or nevi. The groups were homogeneous in terms of demographic and clinical characteristics. An informed consent was signed by all the study participants. The

procedures and the experiments we have done respect the ethical standards in the Helsinki Declaration, as well as national law. The study protocol was approved by the Ethics Committee of the Victor Babes Infectious and Tropical Diseases Hospital (2/18.09.2017) and by the Ethics Committee of the University of Medicine and Pharmacy Carol Davila (149/22.11.2017)

We have recruited patients aged over 18 years with no systemic disorders, with an adequate nutritional status. The exclusion criteria consisted of conditions able to alter and interfere with the parameters of oxidative stress, namely pregnancy, alcoholism, tobacco use, drug abuse, the treatment with corticosteroids, non-steroidal anti-inflammatory drugs, immunosuppressants, the use of vitamins and nutritive supplements. Only patients in the pre-therapeutic phase were enrolled. With regard to HCV positive patients, asymptomatic patients with no signs of active liver disease were selected. All study participants gave their consent to the use of their biological samples in research studies.

We have analyzed 4-HNE as a representative marker of lipid peroxidation, SDMA as a marker of protein alteration and TAC, a marker of antioxidant defense. LP was diagnosed on clinical and histopathological aspects. HCV infection was diagnosed based on the detection of anti-HCV antibodies and viral RNA in the patient blood samples. Blood samples were collected after 12 hours of fasting using a holder-vacutainer system. Venous blood samples collected in tubes containing an anticoagulant (K3EDTA) were used for hematological tests; serum obtained from venous blood collected in vacutainer without an anticoagulant was used for biochemical, serological and immunological determinations. Samples were immediately processed or frozen at -80 degrees Celsius. Hemolyzed or lactescent samples were rejected. 4-HNE, SDMA and TAC were determined by competitive ELISA method. The colorimetric evaluation of the final product was made at a wavelength of 450 nm using a semi-automatic analyzer (Tecan GmbH, Grodig, Austria). The levels of 4-HNE were expressed as $\mu\text{gram/mL}$ serum, the levels of SDMA were expressed as $\mu\text{mol/L}$ and the levels of TAC were expressed as $\mu\text{mol/L}$. The ELISA method is sensible ($< 0.1 \mu\text{gram/mL}$ – 4-HNE, 0.09 nmol/mL – SDMA, $15 \mu\text{mol/L}$ - TAC), reproducible (95–97%), repeatable (variation coefficient under 10%), specific for the analyzed markers, with no significant cross reactivity or interference with others structural

analogs (MBS724354 kit – 4-HNE, Elabscience, USA—E-EL-0042 kit - SDMA, Immunodiagnostic kit – TAC). The samples were analyzed in duplicate.

Statistical analysis

The comparison of data between groups was performed using Kruskal Wallis and the post-hoc test Dunn for pairwise comparisons. We chose a significance level (p) of 0.05 (5%) and a confidence interval of 95% for hypothesis testing.

RESULTS

The demographic characteristics of the subjects were similar. Females were more frequently affected than men in all groups. The majority of the patients were in the age group of 50–70 years (Table 1). The clinical aspects of LP patients and the severity of the disease are presented in Table 2 and Table 3. We have stratified the patients with LP according to the extension of the lesions, using body surface area (BSA) score, in three categories as follows: patients with BSA 0–30%, patients with BSA 30–60%, patients with BSA greater than 60%

There was a progressive decrease in serum 4-HNE levels in the studied groups (Figure 1), as follows: group A – $8.41 \pm 1.11 \mu\text{g/mL}$, group B – $7.97 \pm 2.17 \mu\text{g/mL}$, group C – $7.81 \pm 1.96 \mu\text{g/mL}$ and group D – $6.15 \pm 1.17 \mu\text{g/mL}$. Statistically significant differences were detected between group D and group C ($p < 0.01$), group B ($p < 0.05$), group A ($p < 0.01$) (Table 4).

Figure 1. Serum 4-HNE levels in the studied groups.

A – HCV positive patients with LP, B – HCV positive patients without LP, C – HCV negative patients with LP, D – control group

There was a progressive decrease in serum SDMA levels in the studied groups (Figure 2), as follows: group A – 1.10 ± 0.24 $\mu\text{mol/L}$, group B 1.03 ± 0.16 $\mu\text{mol/L}$, group C – 0.84 ± 0.19 $\mu\text{mol/L}$ and group D – 0.50 ± 0.06 $\mu\text{mol/L}$. Statistically significant differences were detected between group D and group C ($p < 0.01$), group B ($p < 0.01$), group A ($p < 0.01$) In addition, there were statistically significant differences between group A and C ($p < 0.01$) and group B and C ($p < 0.01$) (Table 5).

Figure 2. Serum SDMA levels in the studied groups

A – HCV positive patients with LP, B – HCV positive patients without LP, C – HCV negative patients with LP, D – control group\

There was a progressive increase in serum TAC levels in the studied groups (Figure 3), as follows: group A – 234.50 ± 49.96 $\mu\text{mol/L}$ group B – 255.83 ± 41.41 $\mu\text{mol/L}$, group C – 269.83 ± 43.33 $\mu\text{mol/L}$ and group D – 316.46 ± 29.33 $\mu\text{mol/L}$. Statistically significant differences were detected between group D and group C ($p < 0.01$), group B ($p < 0.01$), group A ($p < 0.01$) (Table 6).

Figure 3. Serum TAC levels in the studied groups

A – HCV positive patients with LP, B – HCV positive patients without LP, C – HCV negative patients with LP, D – control group

There was no correlation between the oxidative stress markers (4-HNE, SDMA and TAC) and LP severity (Table 7)

Table 1
The characteristics of study participants

Parameter	Group			
	A	B	C	D
Male:female ratio	1:3	1:2	1:2.1	1:1.6
Age (years)	57.33 ± 6.11	58.16 ± 6.80	54.25 ± 6.96	53.07 ± 7.26
mean $\pm$ SD_				

A – HCV positive patients with LP, B – HCV positive patients without LP, C – HCV negative patients with LP, D – control group, SD – standard deviation

Table 2
Clinical aspects of LP patients

Group	Cutaneous LP n (%)	Oral LP n (%)	Lichen planopilaris n (%)	Nail LP n (%)
A	12 (100.00)	3 (25.00)	1 (8.33)	1 (8.33)
C	31 (100.00)	5 (16.12)	1 (3.22)	3 (9.67)

A - HCV positive patients with LP, C – HCV negative patients with LP

Table 3
The distribution of LP patients according to the body surface area (BSA) score

Group	BSA		
	0-30% n (%)	30–60% n (%)	>60% n (%)
A	6 (50.00)	5 (41.67)	1 (8.33)
C	15 (48.39)	13 (41.94)	3 (9.68)

A – HCV positive patients with LP, C – HCV negative patients with LP

Table 4
Serum 4-HNE levels in the studied groups (expressed as mean and standard deviation)

4-HNE (µg/mL)	Mean±SD	Median	p value			
			A	B	C	D
A	8.41±1.11	8.15	-	0.34	0.22	<0.01*
B	7.97±2.17	8.10	-	-	0.86	0.017*
C	7.81±1.96	7.80	-	-	-	<0.01*
D	6.15±1.17	6.20	-	-	-	-

4-HNE – 4-hydroxynonenal, SD – standard deviation

A – HCV positive patients with LP, B – HCV positive patients without LP, C – HCV negative patients with LP, D – control group

* statistically significant

Table 5
Serum SDMA levels in the studied groups (expressed as mean and standard deviation)

SDMA (µmol/L)	Mean±SD	Median	p value			
			A	B	C	D
A	1.10±0.24	1.12	-	0.22	<0.01*	<0.01*
B	1.03±0.16	1.04	-	-	<0.01*	<0.01*

Table 5 (continued)

C	0.84±0.19	0.83	-	--	-	<0.01*
D	0.50±0.06	0.51	-	-	-	-

SDMA – symmetric methylarginine, SD – standard deviation

A – HCV positive patients with LP, B – HCV positive patients without LP, C – HCV negative patients with LP, D – control group

* statistically significant

Table 6
Serum TAC levels in the studied groups (expressed as mean and standard deviation)

TAC (µmol/L)	Mean±SD	Median	p value			
			A	B	C	D
A	234.50±49.96	221.00	-	0.34	0.052	<0.01*
B	255.83±41.41	246.00	-	-	0.37	<0.01*
C	269.83±43.33	286.00	-	-	-	<0.01*
D	316.46±29.33	312.50	-	-	-	-

TAC – total antioxidant capacity, SD – standard deviation

A – HCV positive patients with LP, B – HCV positive patients without LP, C – HCV negative patients with LP, D – control group

* statistically significant

Table 7
Serum levels of oxidative stress markers according to body surface area (BSA) score in patients with LP

Parameter	BSA 0-30% (n=14)	BSA 30-60% (n=12)	BSA >60% (n=5)	p value
4-HNE (µg/mL) mean±SD	7.87±2.18	7.88±1.85	7.50 ±1.91	>0.05
SDMA (µmol/L) mean±SD	0.88±0.17	0.84±0.21	0.73±0.19	>0.05
TAC (µmol/L) mean±SD	265.35±49.46	276.25±33.83	267.00±52.74	>0.05

4-HNE – 4-hydroxynonenal, SDMA – symmetric methylarginine, SD – standard deviation

DISCUSSIONS

The inflammatory infiltrate present in LP lesions is the source of excess production of ROS. In addition, ROS can be generated by epidermal keratinocytes under the influence of pro-inflammatory cytokines such as IL-1 and TNF alpha [23]. Numerous studies attest to the link between inflammation and oxidative stress in various diseases such as diabetes mellitus, arterial

hypertension, neoplasms, etc. [24, 25]. The relationship between inflammation and oxidative stress is bidirectional; inflammatory cells release ROS, and in turn ROS can lead to the activation of certain pathways involved in the inflammatory process [26].

Lipid peroxidation was overexpressed in all studied groups compared to controls. The serum levels of 4-HNE, a molecular parameter selected to evaluate the level of lipid peroxidation, were

increased in the patient groups (A, B and C) compared to controls (group D). There were not statistically significant differences between patient groups. However, the highest level was in group A and the lowest level in group C. Consequently, we can speculate that HCV amplifies the oxidative processes in LP. Interestingly, it seems that HCV has the ability to detect lipid peroxides resulting in a decrease in viral replication, a process that can underlie the persistence of HCV [27]. We consider that alterations in antioxidant defence also contribute to the increase in lipid peroxidation level in LP patients with HCV infection. The adducts formed by MDA and 4-HNE with proteins can become immunogens and may result the formation of autoantibodies involved in the pathogenesis of LP [28].

4-HNE is a highly reactive compound due to the three functional groups present in its structure: an aldehyde, a C2-C3 double bond and a secondary alcohol at carbon C4. 4-HNE exerts variable effects on cells. At low concentrations, 4-HNE regulates adaptive signaling pathways and gene expression [29].

The biological activities of 4-HNE are exerted through the regulation of several oxidative stress-sensitive transcription factors (NRF2, NF- κ B, AP-1, etc.) and activation of stress response pathways [19, 30]. 4-HNE may activate or inhibit NF- κ B, a transcription factor that regulates various biological processes, including immune response, inflammation, cell proliferation and apoptosis [31].

HCV induces cell lesions with initiation of oxidative stress and consequently lipid peroxidation [27]. A recent study has evaluated lipid peroxidation in patients with chronic hepatitis C. MDA adducts were observed in 77% of cases and 4-HNE adducts in 30% of cases, indicating the role of lipid peroxidation in HCV infection [32]. Konishi *et al.* investigated the serum levels of 8-isoprostane in patients with hepatic diseases and concluded that lipid peroxidation is increased in patients with non-alcoholic liver steatosis and chronic HCV infection [33]. The core protein in the structure of the virus induces oxidative stress even in the absence of inflammation; an observation resulted from a study on mice [34].

Regarding the serum levels of SDMA, statistically significant differences were identified between the groups of patients (groups A, B, C) and the control group (group D). Statistically

significant differences were also observed between group A and C as well as between group B and C. These results suggest that SDMA is a marker of oxidative stress in both LP and HCV infection and the process is augmented by HCV.

In the past, SDMA was considered an inert metabolite, therefore the data about its role is scarce. However, recent studies have shown that SDMA is involved in many processes such as oxidative stress, apoptosis, inflammation, etc. It seems that SDMA promotes oxidative stress and inflammation by increasing calcium influx into monocytes and by stimulating oxidase activity. SDMA induces the expression of markers of differentiation and adhesion in monocytes and granulocytes, stimulating their adhesion to the endothelium [35].

The investigation of the process of methylation of arginine in the pathogenesis of both LP and HCV could underlie the identification of new pathways involved in the development and the association of the two diseases.

A progressive increase in the serum levels of TAC, from group A to group D, was identified. Thus, the lowest serum levels of TAC were detected in LP patients with HCV infection.

Oxidative stress implies an imbalance between oxidants and antioxidants [1]. The antioxidants prevent the formation of ROS, block their activity and capture free radicals. Antioxidant systems are also involved in the repair of various cellular components damaged by ROS [36, 37]. Low levels of antioxidants such as catalase and vitamin C have been detected in LP patients [38] and recent studies have shown the efficacy of antioxidant agents in LP treatment [39]. Identifying specific pathways for the metabolic regulation of 4-HNE and SDMA levels would be useful in the implementation of new therapeutic options to prevent the onset and progression of LP. The decreased serum levels of TAC identified in LP patients could represent an argument for the implementation of an antioxidant therapy in these patients. The results obtained in our study confirm the hypothesis that the development of LP lesions is a complex process that is influenced by oxidative, infectious, inflammatory and immune mechanisms.

We did not identify an association between the severity of LP and the levels of oxidative stress markers. Our results are in concordance with the results obtained by Hashemy *et al.* [40].

To the best of our knowledge this is the first study to investigate the influence of HCV infection on oxidative stress in LP patients. In addition, this is the first study which has investigated the role of 4-HNE and SDMA in cutaneous LP.

The main limit of the study was that the studied groups included a small number of patients. The assessed parameters can be influenced by a wide range of factors; therefore, the inclusion and exclusion criteria were very strict. In addition, LP is not one of the most common dermatological conditions, and the association with HCV further restricts the number of study participants. The study was unicentric. We consider that a multicenter study including a higher number of participants offers the possibility to generalize the obtained results. Moreover, correlations between oxidative stress markers and viral parameters such as viral load would be interesting.

CONCLUSIONS

In summary, we have found higher serum levels of 4-HNE and SDMA as well as lower serum levels of TAC in LP patients and in those with LP and HCV infection when compared to controls. In addition, we have observed higher levels of 4-HNE and SDMA in association with lower levels of TAC in LP patients with HCV infection than in those without HCV infection. Moreover, both LP and HCV infection are characterized by an imbalance between oxidants and antioxidants. These data show that oxidative stress plays a role in LP pathogenesis and the process is amplified by HCV infection. To the best of our knowledge this is the first study which has investigated the influence of HCV infection on oxidative stress in LP patients. These results may represent the theoretical basis for understanding the LP pathogenesis and its relationship with HCV infection.

Introducere. Lichenul plan (LP) este o afecțiune cutaneo-mucoasă mediată de limfocitele T, de etiologie necunoscută. Există dovezi din ce în ce mai numeroase că stresul oxidativ ar putea juca un rol important în patogeneza LP. Prin urmare, am investigat markeri de stres oxidativ în LP și influența infecției cu virusul hepatitei C (VHC), o afecțiune frecvent asociată, asupra stresului oxidativ la pacienții cu LP.

Metodă. Am determinat nivelurile serice de 4-hidroxinonenal (4-HNE) și dimetilarginină simetrică (SDMA), ca markeri ai stresului oxidativ și nivelul capacității antioxidante totale (TAC), ca marker al apărării antioxidante, în 4 grupuri: grupul A – pacienți VHC pozitivi cu LP ($n = 12$), grupul B – pacienți VHC pozitivi fără LP ($n = 12$), grupul C – pacienți VHC negativi cu LP ($n = 31$) și grupul D – grupul control ($n = 26$).

Rezultate. În rândul pacienților cu LP am identificat un nivel crescut al peroxidării lipidice (4-HNE – grupul A – $8,41 \pm 1,11 \mu\text{g/mL}$, grupul B – $7,97 \pm 2,17 \mu\text{g/mL}$, grupul C – $7,81 \pm 1,96 \mu\text{g/mL}$ și grupul D – $6,15 \pm 1,17 \mu\text{g/mL}$) și modificări ale metilării argininei (SDMA – grupul A – $1,10 \pm 0,24 \mu\text{mol/L}$, grupul B – $1,03 \pm 0,16 \mu\text{mol/L}$, grupul C – $0,84 \pm 0,19 \mu\text{mol/L}$ și grupul D – $0,50 \pm 0,06 \mu\text{mol/L}$), însoțite de apărare antioxidantă diminuată (TAC – grupul A – $234,50 \pm 49,96 \mu\text{mol/L}$, grupul B – $255,83 \pm 41,41 \mu\text{mol/L}$, grupul C – $269,83 \pm 43,33 \mu\text{mol/L}$ și grupul D – $316,46 \pm 29,33 \mu\text{mol/L}$, modificările fiind mai importante când s-a asociat infecția cu VHC).

Concluzii. La pacienții cu LP există un dezechilibru între oxidanți și antioxidanți, dezechilibru accentuat de prezența infecției cu VHC. SDMA ar putea reprezenta un nou biomarker de stres oxidativ în rândul acestor pacienți. Conform documentării noastre, acesta este primul studiu care a investigat influența infecției cu VHC asupra stresului oxidativ la pacienții cu LP.

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