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## Prevalencija sustavnih bolesti i lijekova u bolesnika s oralnim lihenom planusom

### *The Prevalence of Systemic Diseases and Medications in Patients with Oral Lichen Planus*

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#### Sažetak

Lichen planus je kronična imunosna upalna bolest koja često zahvaća sluznicu usne šupljine. Sustavne bolesti i lijekovi smatraju se precipitirajućim čimbenicima u njegovom nastanku. **Svrha rada:** ispitati prevalenciju sustavnih bolesti i lijekova u bolesnika s oralnim lihenom planusom (OLP) i utvrditi njihovu međusobnu povezanost. **Materijal i metode:** anamnestički podatci uzeti su retrospektivno iz medicinskih kartona 145 bolesnika s OLP-om od čega 104 žene i 41 muškarca koji su radi liječenja OLP-a upućeni na Zavod za oralnu medicinu. U svih je bolesnika dijagnoza OLP-a postavljena na temelju kliničkih i histopatoloških kriterija. Podatci o sustavnim bolestima i lijekovima u bolesnika s OLP-om bilježeni su za period od dvije godine (jesen 2007.- jesen 2009.) i uspoređeni sa prevalencijom sustavnih bolesti i najčešće korištenih lijekova u bolesnika s oralnom leukoplakijom (LPL) kao i s podacima opće populacije prema nacionalnom registru bolesti. Svi su podatci obrađeni primjenom  $\chi^2$  testa, s razinom značajnosti od  $p < 0,05$ . **Rezultati:** sustavne bolesti imalo je 77,9% bolesnika s OLP-om; značajno više nego bolesnika s LPL, pri čemu je najučestalija bolest bila hipertenzija. Hipertenzija je najučestalija bolest u općoj populaciji prema podacima iz nacionalnog registra. **Zaključak:** sustavne bolesti učestalije su u populaciji pacijenata s OLP-om u odnosu na LPL, pri čemu se veća prevalencija hipertenzije među bolesnicima s OLP-om ne može smatrati etiološkim čimbenikom za razvoj OLP-a jer hipertenzija prevalira i u općoj populaciji.

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#### Ključne riječi

oralni lichen planus; leukoplakija;  
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#### Uvod

Lichen planus je kronična upalna bolest kože i sluznica koja često zahvaća i sluznicu usne šupljine. Točan etiopatogenetski mehanizam nije razjašnjen, ali postoje dokazi koji upućuju da je riječ o poremećaju imunološkog sustava (1). Sustavne bolesti i lijekovi smatraju se čimbenicima koji potiču nastanak oralnog lihen planusa (OLP). Mnogobrojna istraživanja upućuju na to da pacijenti s OLP-om imaju češće šećernu bolest (2,3) i bolesti jetara negoli oni bez OLP-a. No, postoje i suprotna mišljenja (4,5). Neki stručnjaci ističu povezanost lihen planusa i virusa hepatitisa C (6-12), a drugi je isključuju (13-15).

Povezanost OLP-a s hipertenzijom nije razjašnjena, i podatci su raličiti. Eisen i Xue sa suradnicima nisu pronašli povezanost OLP-a s bolestima srca i krvnih žila (1,16). U istraživanju Cebecia i suradnika u kojoj je sudjelovalo pet tisuća odraslih Turaka, nije nađena povezanost između sustavnih bolesti i lezija sluznice usne šupljine. Među svim ispitanim lezijama, oralni lichen planus i leukoplakija (LPL) pronađeni su u 2,2% ispitanika (17).

#### Introduction

Lichen planus is a chronic inflammatory disease of the skin and mucous membranes that frequently involves oral mucosa. The exact aetiopathogenesis has not been clarified, but the immunological system is believed to play a leading role (1). Systemic diseases and medications are considered to be precipitating factors in the development of oral lichen planus (OLP). A number of previous reports have suggested that patients with OLP have associated diabetes (2,3) and liver diseases more often than patients without OLP. Conversely, some reports have not supported these presumptions (4,5). Also, some authors have reported association between lichen planus and hepatitis C virus (6-12) which was not confirmed by others (13-15).

Association of OLP and hypertension remains unclear and controversial. Eisen and Xue and al. have found no association between OLP and cardiovascular diseases (1,16). In the study of Cebeci et al. that comprised 5000 Turkish adults no relation was found between systemic diseases and oral mucosal lesion occurrence. Among all examined lesions OLP and leukoplakia (LPL) were observed in 2,2% of the patients (17).

Lijekovi i stres također su čimbenici za koje se vjeruje da potiču razvoj OLP-a. U Eisenovoj studiji stres je zabilježen kao najučestaliji uzrok akutne egzacerbacije OLP-a (16).

Posljednjih godina u literaturi mnogo je opisa slučajeva oralne lihenoidne reakcije na inhibitore enzima konvertaze angiotenzina i nesteroidne antiupalne lijekove (NSAUL-e). Često se kao mogući uzroci lihenoidne reakcije spominju i oralni hipoglikemici, penicilamin te zlato (18). No, još nisu definirana histološka obilježja prema kojima se lihenoidnu reakciju može pouzdano razlikovati od oralnog lihenoida i drugih lihenoidnih lezija (19). Zato se potvrda dijagnoze oralne lihenoidne reakcije temelji samo na kliničkim kriterijima.

Svrha ovog rada bila je ispitati prevalenciju sustavnih bolesti i uzimanja lijekova u bolesnika s OLP-om i ustanoviti njihovu moguću uzročnu povezanost.

Usporedba s podacima iz opće populacije trebala je pokazati ima li prevalencija pojedinih bolesti kod OLP-a etiološki značaj ili je samo refleksija bolesti u općoj populaciji.

### Ispitanici i postupci

Podatci su prikupljeni retrospektivno iz kartona 145 pacijenata, 104 žena i 41 muškarca koji su upućeni na Zavod za oralnu medicinu Stomatološkog fakulteta Sveučilišta u Zagrebu. U istraživanje su bili uključeni ispitanici koji su ispunjavali kliničke i histopatološke kriterije (18) za dijagnozu OLP-a. Ispitanici koji su ispunjavali kriterije za lihenoidnu reakciju na amalgam nisu bili uključeni. Podatci su se skupljali dvije godine (od jeseni 2007. – do jeseni 2009.) Medicinski podatci uzeti iz anamnestičkih kartona svakog ispitanika obuhvaćali su: kliničku sliku OLP-a, sustavne bolesti (hipertenzija, šećerenu bolest, bolesti jetara i ostale bolesti, primjerice, gastrointestinalne, bolesti štitnjače, krvi, psihijatrijske, alergije i infekcije). S obzirom na to da su bolesti u skupini „druge bolesti“ bile manje učestale, prikazane su zajedno u jednoj skupini. Zabilježeni su i podatci o lijekovima koje su ispitanici uzimali. Sve to zabilježeno je i za ispitanike kontrolne skupine koja je obuhvaćala 137 bolesnika s leukoplakijom (LPL-om). Podatci o tome koliko su česte sustavne bolesti uspoređeni su između skupina ispitanika s OLP-om i LPL-om te s učestalošću sustavnih bolesti u općoj populaciji prema podacima iz nacionalnog statističkog registra (20-22). Za kontrolnu skupinu bili su odabrani bolesnici s leukoplakijom (LPL) zbog njezine kliničke sličnosti s lihenom planusom te dokazane različite patogeneze tih dviju bolesti. Ispitanici s LPL-om prema dobi su odgovarali ispitanicima s OLP-om. Statistička analiza uključivala je deskriptivnu statistiku i  $\chi^2$  test, a obavljena je pomoću SPSS-verzije 16.0 za Windows. Razina značajnosti od  $p < 0,05$  smatrala se statistički značajnom.

### Rezultati

Srednja dob ispitanika s OLP-om bila je 51 godinu ( $\pm 17$ ), a srednja dob ispitanika s LPL-om 49 ( $\pm 18$ ). Naši rezultati pokazali su da ispitanici s OLP-om imaju najčešće jednu ili više sustavnih bolesti – dokazane su u 77,9% ispitanika. Naj-

Drugs and stress are also factors which are believed to be included in the development of OLP. In the study of Eisen stress was reported as the most frequent cause of acute exacerbations of OLP (16).

More recently, the literature has been replete with case reports and a few limited studies of oral lichenoid drug reactions to angiotensin-converting enzyme inhibitors and non-steroidal anti-inflammatory drugs (NSAIDs). However, oral hypoglycemic drugs, penicillamine and gold have also been frequently implicated (18). There are no clear or distinct clinical or histological features that reliably distinguish oral lichenoid drug reactions from oral lichen planus or other lichenoid lesions (19). Therefore, confirmation of the diagnosis of oral lichenoid drug reactions remains problematic.

The purpose of this study was to examine the prevalence of systemic diseases and medications in patients with OLP and to determine their possible causal relationship.

Comparison with data from the general population was aimed to determine whether the prevalence of certain diseases in OLP patients have etiological significance or is a reflection of the prevalence of diseases in general population.

### Material and Methods

Retrospective data included medical records of 145 patients, 104 women and 41 men who were referred to the Department of Oral Medicine, School of Dental Medicine, University of Zagreb. All patients had clinical and histopathological criteria fulfilled (19) for diagnosis of OLP. Patients in whom criteria for lichenoid reaction to amalgam were fulfilled were excluded. Data were collected for the period of two years (autumn 2007- autumn 2009). Type of OLP, systemic diseases (hypertension, diabetes, liver diseases and other diseases that included gastrointestinal, thyroid, blood, psychiatric diseases, allergies and infections) were recorded. Since other diseases were of low frequency, they were presented in one group termed „other diseases“. Used medications were recorded in a questionnaire for each patient. Data on the use of drugs and prevalence of systemic diseases were also recorded in the control group which included 137 patients with LPL. These data were compared between OLP and LPL group and compared with Croatian population according to the national statistical register (20-22). Control group included patients with leukoplakia because of clinical similarities with OLP and proved different pathogenesis of these two diseases. Patients with LPL were age-matched with OLP patients. Statistical analysis, which included descriptives and  $\chi^2$  test was performed using SPSS version 16.0 for Windows and  $p < 0,05$  was considered statistically significant.

### Results

The mean age of patients with OLP was 51 ( $\pm 17$ ) and mean age of patients with LPL was 49 ( $\pm 18$ ). Our results have shown that patients with OLP mostly have one or more systemic diseases. Systemic diseases associated with OLP were

učestalija je bila hipertenzija (46% ispitanika), a slijede bolesti jetara i šećerna bolest. Najčešći oblik OLP-a bio je retikularni (80,6%), a zatim erozivni (18,7%) i bulozni (0,7%).

Dokazana je statistički značajna razlika u raspodjeli sustavnih bolesti između ispitanika s OLP-om u odnosu na kontrolnu skupinu s leukoplakijom (Tablica 1).

Također je dokazana statistički značajna razlika između ispitanika s OLP-om i LPL –om koji nisu uzimali lijekove; značajno više ispitanika koji nisu uzimali lijekove bilo je u kontrolnoj skupini s LPL-om (Tablica 2). Suprotno tome, između ispitanika s OLP-om i LPL-om koji uzimaju lijekove nije bilo statistički značajne razlike.

**Tablica 1.** Prevalencija sustavnih bolesti u bolesnika s OLP-om i LPL-om

Table 1	OLP	LPL	p*
The prevalence of systemic diseases in patients with OLP and LPL			
Visoki tlak • Hypertension	67	46	0,028
Šećerna bolest • Diabetes mellitus	22	9	0,026
Bolesti jetre • Liver diseases	41	12	<0,0001
Ostale bolesti • Other diseases	20	72	<0,0001
Bez sustavnih bolesti • No systemic diseases	32	41	0,058
Ukupno • Total	182	180	

\*  $\chi^2$  test

## Rasprava

Najčešća bolest u ispitanika s OLP-om je hipertenzija u (46%), a slijede bolesti jetara i šećerna bolest.

Općenito, u ispitanika s OLP-om prevalencija sustavnih bolesti uključujući hipertenziju i šećernu bolest bila je viša nego u ispitanika s leukoplakijom. Usporedba prevalencije sustavnih bolesti u ispitanika o OLP-om s podatcima Hrvatskog zdravstveno-statističkog ljetopisa iz 2006. godine (21) te nedavno provedene probirne prospektivne studije koja je uključivala ispitanike s hipertenzijom u ordinacijama obiteljske medicine (20), pokazuje da je hipertenzija najčešća bolest u općoj populaciji (37,5%), ali učestalost po pojedinim županijama varira (29%–43,5%). Naši su rezultati u skladu s rezultatima Xue i suradnika i Eisena – oni nisu pronašli razlike u prevalenciji bolesti srca i krvnih žila u bolesnika s OLP-om u odnosu prema općoj populaciji (1,16). Uspoređujući naše rezultate s rezultatima usporedne retrospektivne studije Thongprasom i suradnika koja je uključivala hrvatske i tajlandske ispitanike s OLP-om, evidentno je da prevalencija hipertenzije u bolesnika s OLP-om odgovara prevalenciji u općoj populaciji. U istoj studiji dokazano je da je u bolesnika s bolestima jetara najčešći atrofično-erozivni oblik OLP-a (23). No, naši su rezultati oprečni rezultatima Cekić-Arambašin i suradnika (24). U njihovoj studiji najčešće bolesti bile su gastritis, bolesti jetara i žuči te šećerna bolest. Hipertenzija je zabilježena tek u manjeg broja ispitanika (2%). Te se razlike mogu objasniti činjenicom da su se u proteklih deset godina promijenili dijagnostički kriteriji za hipertenziju te da su bolesnici danas vjerojatno svjesniji nužnosti brige o zdravlju pa su mnogi slučajevi ranije otkriveni. Bolesti jetara bile su

found in 89% of patients. Predominant disease was found to be hypertension which is present in 37% of our patients, followed by liver diseases and diabetes. The most frequent form of OLP was reticular (80,6%), followed by erosive (18,7%) and bullous (0,7%).

Statistically significant difference was found in distribution of systemic diseases between OLP patients and control group which is shown in Table 1.

Statistically significant difference was found between patients who took no medications among OLP and LPL patients which is shown in Table 2. No statistically significant difference was found between taken medications among OLP and LPL patients.

**Tablica 2.** Raspodjela lijekova koje su uzimali bolesnici s OLP-om i LPL-om

Table 2	OLP	LPL	p*
Distribution of taken medications in patients with OLP and LPL			
Antihipertenzivi • Antihypertensives	38	41	0,637
Nesteroidni antiupalni lijekovi (NSAUL) • Nonsteroid antiinflammatory drugs (NSAIDs)	20	17	0,328
Drugi lijekovi • Other medications	59	64	0,498
Ne uzimaju lijekove • Took no medications	28	54	0,028
Ukupno • Total	145	176	

\*  $\chi^2$  test

## Discussion

The predominant disease found in OLP patients was hypertension which is present in (46%) of our patients, followed by liver diseases and diabetes.

The incidence of systemic diseases including hypertension and diabetes in OLP patients was higher than the prevalence of these diseases in patients with leukoplakia. When compared the prevalence of systemic diseases in OLP patient with the data from Croatian Health Service Yearbook 2006 (21) and recent large prospective study which included screening for hypertension in general medicine dispensary (20), we can see that hypertension is the most common disease in the general population (37.5%) but its frequency varies in different counties (29%–43.5%). Our results are corresponding with the results of Eisen and Xue et al. who found no cardiovascular diseases in patients with OLP and general population (1,16). When compared with the results from comparative retrospective study of Thongprasom et al. which included Croatian and Thai patients with OLP, the prevalence of hypertension in OLP patients also correspond with the prevalence in the general population. In the same study, it was shown that in patients with liver diseases the most common type of OLP was atrophic-erosive type (23). However, our results are contrary to the results of Cekić-Arambašin et al (24). In their study, the most common diseases were gastritis, liver and gallbladder diseases and diabetes. Hypertension was present only in the minority of patients (2%) at the last place. These differences could be explained by the fact that diagnostic criteria for the hypertension have been changed during the last ten years and patients today are probably more aware of their health condition so many

učestalije u naših ispitanika s OLP-om nego s LPL-om. Čini se da povezanost OLP-a s infekcijom virusom hepatitisa C i bolestima jetre ovisi o zemljopisnim čimbenicima (16). Hrvatski bolesnici s OLP-om, kao dio mediteranske populacije češće imaju bolesti jetara (22%) nego što se bilježi u općoj populaciji (2,2%) (21). Iako su neki autori (25-27) izvijestili da je probir za kronične bolesti jetre i HCV-a u bolesnika s OLP-om u rutinskoj dijagnostici kontroverzan, u skladu s našim rezultatima, on može biti koristan u ranoj dijagnostici. Autori Ali i Suresh (3) također su izvijestili da OLP može biti povezan s povišenim vrijednostima jetrenih transaminaza. No, nisu ustanovili povezanost između OLP-a i HCV-infekcije. I šćerna bolest je dokazana u višem postotku u bolesnika s OLP-om nego LPL-om, što upućuje na to da se rutinskim određivanjem razine glukoze u krvi može otkriti bolesnike s još nedijagnosticiranom šćernom bolešću te ih dalje pratiti.

Lijekovi koje hrvatski bolesnici s OLP-om najčešće uzimaju su antihipertenzivi i zatim nesteroidni antiupalni lijekovi (NSAUL-i). Antihipertenzivi su također najčešći lijekovi u općoj populaciji (22). Među bolesnicima s OLP-om i LPL-om nema statistički značajne razlike prema vrstama najčešće propisanih lijekova, premda je statistički značajno više bolesnika s LPL-om koji uopće ne uzimaju lijekove u odnosu na bolesnike s OLP-om.

## Zaključak

Veća prevalencija hipertenzije među ispitanicima s OLP-om ne može se smatrati etiološkim čimbenikom za nastanak OLP-a budući da je hipertenzija i u općoj populaciji najčešća bolest. OLP se također ne može izravno povezati s određenim lijekom premda se u određenim slučajevima treba isključiti lichenoidna reakcija.

## Zahvala

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cases are diagnosed earlier. Liver diseases were more common in our OLP than in LPL patients. It seems that OLP with both HCV infection and liver disease appears to be dependent on geographic factors (16). Croatian patients, as Mediterranean population, have OLP associated with liver diseases more often than the general population (2.2%) (21). Although some authors (25-27) have reported that screening for chronic liver disease and hepatitis C in the routine assessment of a patient with OLP is controversial, according to our results, routine screening of patients with OLP may be useful in early diagnosis of liver diseases. Ali and Suresh (3) have also reported that OLP might be related to elevated transaminase level. However, no correlation between OLP and HCV infection could be assessed in their study. Diabetes was also found in higher percent in OLP than in LPL patients which alert that routine blood glucose level could be useful in detecting patients with undiagnosed diabetes and monitoring.

The most commonly used medications in Croatian OLP patients were antihypertensives followed by non-steroid anti-inflammatory drugs. Antihypertensives are also the most commonly used medications in the general population (22). There is no statistically significant difference between taken medication in OLP and LPL patients, except those patients who took no medications which was higher in LPL group. This could alert that certain percent of patients did not take their medications properly.

## Conclusion

Increased prevalence of hypertension among OLP patients in comparison to the prevalence in the general population can not be interpreted as the etiological factor for the development of OLP.

OLP could not be directly connected with the certain medication, although, in suspected cases, oral drug lichenoid reaction should be considered.

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## Abstract

Lichen planus is a chronic immunologic inflammatory disease that frequently involves oral mucosa. Systemic diseases and medications are considered to be precipitating factors in the development of oral lichen planus. **Objective:** The purpose of this study was to examine the prevalence of systemic diseases and medications in patients with oral lichen planus (OLP) and to determine possible causal relationship. **Materials and methods:** Retrospective data included medical records of 145 patients, 104 women and 41 men who were referred to the Department of Oral Medicine. All patients had clinical and histopathological criteria fulfilled for diagnosis of oral lichen planus. Data were collected for the period of two years (autumn 2007- autumn 2009). These data were compared with the prevalence of systemic diseases in patients with oral leukoplakia (LPL) and general Croatian population according to the national statistical register. The same comparison was made for the used medications. Obtained data were analyzed by use of  $\chi^2$  test with level of significance  $p < 0,05$ . **Results:** Systemic diseases associated with OLP were found in 77.9% of patients. The most frequent disease was hypertension. Frequency of systemic diseases between patients with OLP and LPL has shown statistically significant difference. **Conclusion:** Increased prevalence of hypertension among OLP patients in comparison to the prevalence in the general population can not be interpreted as the etiological factor for the development of OLP since hypertension is the most prevalent disease in general population.

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### Key words

Lichen Planus, Oral; Leukoplakia; Hypertension; Diseases, Systemic

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