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Article

Effects of Comorbid Disease Improvement on Oral Lichen Planus (OLP) and Oral Leukoplakia (OL) Lesions: A Retrospective Longitudinal Study

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Abstract: *Background*: Longitudinal studies that investigate the effects of the betterment of comorbid diseases on oral potentially malignant lesions are not yet available. Thereby, the aim of the current study is to examine the effects of comorbid disease betterment on oral potentially malignant lesions' healing both in OLP and OL patients. *Methods:* The data of 197 consecutive patients (144 females and 53 males, age ± SD: 55.19±12.37 years, with ranges: 23-91 years), with oral lesions considered OLP and OL were processed and evaluated. Frequency of comorbid diseases and the presence of HPV (here subtypes were not evaluated) in the lesions in OLP, OL patient groups were evaluated and compared to the results of controls (n=139). Any risk model for OLP and OL lesions were established. High risk model for erosive-atrophic OLP and non-homogenous OL were also described. The influence of the betterment of comorbid diseases were also evaluated. Lesions were scored at the first and at the last visit (full recovery=0, improvement=1, no improvement=2). *Results*: One-hundred and ninety-seven patients (144 OLP +53 OL) were followed up for the average of 47.66 months (min-max: 1-203 months, SD: 54.19). Based on the established models HPV infection, iron deficiency, diabetes, and thyroid function disorders seem to behave as risk factors for OLP and also may affect OL formation. The betterment of comorbid diseases can cause significant improvement of OLP and OL lesions. *Conclusion*: By meticulous follow up of comorbid diseases the betterment of OLP and OL lesions can be achieved.

Keywords: oral lichen planus; oral leukoplakia; HPV; comorbid disease; prevention of cancer formation

1. Introduction

Oral cancer development is a worldwide healthcare problem (https://gco.iarc.who.int/media/globocan/factsheets/cancers/1-lip-oral-cavity-fact-sheet.pdf). The appearance of oral precancerous lesions or as nowadays more preferred oral potentially malignant lesions precedes the development of oral cancers. One third of developed oral cancers is originating from previously diagnosed, and followed up oral precancerous lesions [1].

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The potentially malignant oral lesions most often leading to cancer formation are oral lichen planus (OLP) and oral leukoplakia (OL). In case of OLP tumour progression occurred from 0.44-2.29% of cases [2,3] . While in case of OL a meta-analysis had shown about 4.47-10.74% of OL cases progressing to oral cancer. The highest malignancy rates of potentially malignant lesions were shown in Asia. Being atrophic and/or erosive on the long term the lesion had higher probability to progress to malignancy. Thereby, non-homogeneous OL and erosive OLP have higher probability to turn malignant. Additional risk factors were smoking, drinking alcohol, being a male, and in some studies having HCV infection also increased the malignant potential [2,4]

Nowadays potentially malignant lesion treatment can be described as the elimination of all recognized local factors, parallel the application of topically administered drugs, or excision of the lesion if it has a smaller size. Afterwards in routine medical practice the thorough follow-up of lesions is conducted to intervene into their progression as early as possible [5]. As mentioned before the presence of atrophy and erosion, which means an increased cell death rate in the lesion with higher probability of mistakes in cell division also increases the probability of cancerization.

The mainstream, and as well as the hardship of potentially malignant lesion therapy, as in most therapies, is the cooperation of the affected patient. If they do not want to get rid of smoking or drinking or does not intend to keep good oral hygiene: it is hard to eliminate or to improve the condition of oral potentially malignant lesions. Earlier, in case of OLP it was stated that "local topical treatments were also not the most successful therapies; practically they were not superior to placebo [6,7]. Currently the situation has not improved at all. Though biological therapies have emerged to the everyday practice in multiple specialties their side effects, and their safety is still not carefully examined, especially in case of potentially malignant lesions [7] .

In case of OLP the use of some drugs (like steroids, calcineurin inhibitors, retinoids, anti-tumour necrosis factor (TNF) α therapies) must be done with serious precautions both for topical, oral or intravenous use, because they have deteriorating effects on certain comorbid diseases like hypertension and diabetes, or in some cases they are fully contraindicated (breast feeding). In case of tacrolimus, pimecrolimus, which are calcineurin inhibitors, long term use may also initiate cancer formation, and they are not exceptional amongst biological therapies with this type of potential. At least they can be used as acute solutions to reduce length of severe outbreaks and alleviate related pain [8]. The other controversy that exists with anti-TNFα biological therapies (which is also might be a treatment option in OLP cases), that they may cause OLP formation as a result of reducing TNFα levels, with the parallel increase in interferon α (IFN) level which can create such an environment that is favoured by T cell proliferation, leading to OLP eruptions [9] . Practically the same phenomenon occurs when patients with infectious (HBV, HCV) hepatitis get antiviral therapy by administering ribavirin and IFN α, which also creates an environment favoured by T lymphocytes. OLP eruptions are also common even in this case.

In case of OL even the complete elimination of all known etiological factors can lead to partial healing, both in quantity and quality [10]. In the 60s and the 70s human papilloma viruses (HPV) and their role in cancer formation were still in the shadow, but alcohol consumption, bad oral hygiene and smoking habit were already amongst the known risk factors. Hypothetically, proper treatment that involves all previously known etiological factors could have eliminated these lesions. Reviews on OL treatment options state that the active treatment with vitamin A, bleomycin, β carotene and lycopene does not reduce the possibility of cancer formation more than placebo, despite sometimes they do provide at least temporary improvement[11,12] .

In case of OLP the relationship with comorbid diseases is already known [13]. In case of OL the effects of comorbid diseases are not that obvious, though the connection is more than probable, and cooperation of etiological factors of OL and systemic diseases is not equal to impossible [14]. Longitudinal studies that investigate the effects of the betterment of comorbid diseases on oral potentially malignant lesions are not yet available. Thereby, the aim of the current study is to examine the effects of comorbid disease betterment on oral potentially malignant lesions' healing both in OLP and OL patients.

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Hypothesis: The betterment of comorbid diseases is going to improve OLP and OL lesions in patients.

Steps to take:

1. To determine the frequency of comorbid diseases in OLP, OL patient groups and compare it to a group of patients who were oral mucosa lesion free. Is the frequency of comorbid diseases higher in any of the groups (OLP, OL, control)?
2. To decide whether certain diseases are more frequent in OLP with erosive atrophic subtypes, or in patients with non-homogenous OL?
3. To establish an any risk model for OLP and OL lesions, and to establish a high risk model for erosive atrophic OLP and non-homogenous OL, and to establish a risk model for specific locations (gingiva and lip involvement) of the previously mentioned lesions.
4. To examine whether the betterment of comorbid diseases had any effect on OLP or OL lesion improvement? What were the outcomes?

2. Materials and Methods

2.1. Patients and Investigations

Between 1996 1st January and 2016 31st December the data of 197 consecutive patients (144 females and 53 males, age ± SD: 55.19±12.37 years, with ranges: 23-91 years), with oral lesions considered OLP and OL attending at the Department of Periodontology, Faculty of Dentistry, Medical and Health Science Centre, University of Debrecen, were processed and evaluated in this study. Investigations were performed after having obtained written informed consent from the patients. The study was approved by the local clinical ethical committee of the university (Ethics Cometee-2247-2004, Debrecen, 08-11-2004). Though in this study data were collected in a retrospective manner: clinical description of lesions [15–17] involving types and location on oral mucosa, histological results with detailed descriptions, patients' history, results of repeated blood testing, HPV cytology [18], patch test results for dental materials were also available for these patients (Table 1). HPV, EBV, TTV detailed data of this patient group, cytology and examination methods were published earlier [19–21]. Current detailed data of virus prevalence are not shown in this study. Only the presence in the lesion, except healthy mucosa patients, (+/-) as a datum was used for model establishment. Testing for anti-HbsAg, anti-HbcAg, anti-HbeAg, and anti-HCV was also done, except already diagnosed disease. Previous tumours (patient history), and tumours found throughout the course of the study were also registered.

Table 1. Patient investigations.

1. Medical History	In query for current complains, targeted questioning and survey of available medical documents
2. General physical examination	Inspection, palpation, auscultation, measurement of weight and height, pulse rate and blood pressure (R/R)
3. Oral and dental examination	Inspection of mucous membranes Dental charting – registration of materials Taking mucosa samples with Cytobrush for HPV testing
4. Blood tests	CRP, ASO CBC, DBC, concentration of serum iron, transferring, ferritin, vitamin B12 and folate 'Liver Function' test: serum bilirubin level (direct + total), activities of ALT, AST, GGT and LDH enzymes

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	Antibodies against HBC and HCV were also examined. T3, T4, sTSH levels and serum levels of anti-TPO and TG cholesterol, LDL, HDL, triglycerol levels were measured Fasting blood glucose level
5. Allergy test	Patch test for hypersensitivity reaction towards dental materials
6. Histology	HE stains of biopsy specimens and immunofluorescence labelling in case of bullous forms of OLP
7. Special examinations	In case of patients with erosive-atrophic lichen lesions and negative blood, and allergy test results –were referred to specialist for searching for hidden ailments, such as tumours and autoimmune diseases, involving the specific diagnostic methods.

Patient care involved symptomatic local therapy of the oral lesions provided by the dentist participating in the study and *lege artis* treatment of the coinciding systemic diseases performed by the general practitioners of the patients or by competent specialists. Topical antiseptic treatment, analgesics, and gels that physically protect eroded surfaces were applied to prevent bacterial and/or fungal superinfection of erosive OLP lesions or non-homogenous OL. Application of local corticosteroid, vitamin A oil, calcineurin inhibitors, and other preparations and systemic therapy, intended to treat the oral lesions, were avoided. Patients were requested to return for follow-up exams at every 3 months. Deterioration and recurrence of the lesions, as well as the emergence of any novel complaint was an indication for an immediate check-up. All these were described in patients' documents. Presence of non-plaque induced gingival inflammation; named desquamative gingivitis and lip involvement was also registered.

Results of repeated check-ups were also extracted from files made by the patients' other specialists. During check-up examinations, the patients' notes from other specialists was requested and introduced to the dental check-up notes, as well. Improvement in results by comparing repeated values of tests, in terms of systemic diseases, or oral lesions was scored (full recovery=0, improvement=1, no improvement=2). Presence of lesions was scored: no clinical lesion=0, non-erosive-atrophic OLP or homogenous OL=1 and erosive-atrophic OLP or non-homogenous OL =2 as in a previous study [17].

2.2. Control Subjects

One hundred and thirty-nine subjects (96 females and 43 males, with the age ± SD: 52.52±14.06, min-max: 16-82) with intact oral mucosa and no oral complaints were enrolled in the study. History of previous and currant diseases, together with blood test results were registered.

2.3. Statistics

Patients were classified according to oral diagnosis. For statistical evaluation binary data were collected except age, and follow-up time. Prevalence of comorbid diseases and presence of HPV had been evaluated (HPV detailed data not shown here). Between-group differences were also tested (ANOVA, Tukey's post hoc test). Possible associations between the presence of OLP and OL lesions and coinciding systemic diseases (any risk and high risk models), anatomical localization of lesions (gingiva, lip), HPV infection were assessed by binary logistic regression analysis. Comparison of treatment results was done with paired-sample t-tests. Relationship between the improvement scores

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of systemic disease and the improvement scores of lesions was done by Spearman rank correlation. The SPSS version 20.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

3. Results

3.1. Group Characteristics and Comorbid Disease Prevalence

One-hundred and forty-four OLP patients (mean age ± SD: 54.56±12.37, min-max: 23-80, 109 females and 35 males) and 53 OL patients (mean age ± SD: 56.91±12.31, min-max: 29-91, 35 females and 18 males) were enrolled in the study. The control group had the mean age ± SD: 52.52±14.06, min-max: 16-82 yrs, 96 females, and 43 males). Ninety-three (64.5%) patients had non-erosive, non-atrophic form, while 51 (35.5%) patients had atrophic-erosive form of OLP. Thirty-six (67.9%) OL patients had homogenous, whilst 17 OL patients (22.1%) had non-homogenous form of OL (Table 2).

As seen in the frequency table with percentiles, the most common diseases found in OLP, OL, and control groups were cardio-vascular diseases, including hypertension, fibrillation, valve problems, and e.g. (CVD). Eighty OLP patients (55%), 26 (49 %) OL patients and 57 (41.7%) control subjects had CVD. The prevalence of CVD in both diseased groups statistically was the same.

The frequency of other diseases (Table 2) or conditions that also did not show significant difference ($p>0.05$) between groups were smoking ($p=0.79$), anaemia ($p=0.29$), vitamin B deficiency ($p=0.1$), hyperlipidaemia ($p=0.09$), thyroiditis (Hashimoto and Graves) ($p=0.55$), the frequency of systemic autoimmune diseases (involving Sjögren sy, Raynaud sy., rheumatoid arthritis, mixed connective tissue disease) ($p=0.08$), and allergy to dental materials (nickel, thiomersal, phenilmercuribate, and mercury allergies occurred)) ($p=0.76$).

Significant difference ($p<0.05$) existed between control group and patients' groups in case of prevalence of HPV ($p=0.00$), and iron deficiency ($p=0.00$). In case of OLP patients the frequency of diabetes (both type I. and II.) ($p=0.01$), and thyroid function disorders (hypo- and hyperfunction) ($p=0.05$) were significantly higher amongst OLP patients than in OL patients and controls. In OL patients the only significant difference from the other two groups existed in case of liver function disorders (involving mostly toxic hepatitis cases, and a few cases of infectious hepatitis: there were 2 cases of chronic active hepatitis (HCVRNA positive) amongst the 3 anti-HCV positive cases ($p=0.02$) (Table 2).

There was no significant difference in the prevalence of previously found tumours ($p=0.16$), and also there was no difference by post hoc test between groups. In OLP patients' previous findings included 4 low and high grade epithelial cervical epithelial lesions, 1 mammal, 1 melanoma, 1 colon tumour, 1 OSCC of the buccal mucosa occurred while in OL patients 1 meningeal, 1 endometrium tumour was revealed earlier. During the course of the current diagnostic procedure 1 kidney, 1 prostate tumour was found. By their removal the OLP lesion regrediated to non-erosive-non-atrophic state.

In both patients' group desquamative gingivitis or gingival location and lip involvement was also present. In the OLP group 25/144 (17.3%) patients had desquamative gingivitis, and 8/144 (5.5%) patients had lip involvement. In the OL group 8/53 (20.7%) patients had gingival involvement, and 2/53 (3.7%) had lip involvement. There was no significant difference between OLP and OL groups in terms of the prevalence of gingival and lip involvement (Table 2).

Table 2. Prevalence of comorbid diseases in the study groups (values with significant differences presented with **bold and underlined numbers**).

	control n=139(%)	**OLP n=144(%)**	**OL n=53 (%)**	**Total OLP+OL (n=197)**
non-erosive/erosive OLP; homogenous-non-homogenous OL	-	93/51	36/17	-

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currant smoker	7 (5)	10 (6.9)	5 (9.4)	15
cardiovascular diseases	57(41)	80 (55)	26 (49)	106
anaemia	24 (17.2)	49 (34)	16 (30)	55
iron deficiency	**15 (10.7)**	**54 (37.5)**	**19 (35.8)**	63
Vitamin B deficiency	8 (5.7)	8 (5.5)	6 (11.3)	14
diabetes	6 (4.3)	**33 (22.9)**	5 (9.4)	38
liver disorder	12 (8.6)	32 (22.2)	**16 (30.1)**	48
thyroiditis	0 (0)	12 (8.3)	4 (7.5)	16
thyroid function	10 (7.1)	**38 (26.3)**	10 (18.8)	48
desquamative gingivitis	0 (0)	25 (17.3)	8 (15)	33
lip involvement	0 (0)	8 (5.5)	2 (3.7)	10
autoimmune disease	7 (5)	27 (18.7)	11 (20.7)	38
allergy to dental materials	6 (4.3)	6 (4.1)	2 (3.7)	8
HPV present in lesion cells (except controls: buccal mucosa and tongue)	**2 (1.4)**	**40 (27.7)**	**19 (35.8)**	59

Prevalence of comorbid diseases in OLP subtypes (non-erosive –non atrophic and erosive-atrophic types), and in OL subtypes (homogenous and non-homogenous subtypes).

Comparison of comorbid disease prevalence in OLP and OL subtypes revealed that only diabetes prevalence is significantly different (p=0.004) different between OLP subtypes. All other diseases have not shown significant differences between subtypes (Table 3)

Table 3. Prevalence of comorbid diseases in OLP and OL subtypes (values with significant differences presented with **bold and underlined numbers**).

	non-erosive-non-atrophic OLP (n=93)	**erosive-atrophic OLP (n=51)**	**homogenous OL (n=36)**	**non-homogenous OL (n=17)**
currant smoker	2 (2.1)	3 (5.8)	8 (22.2)	2 (11.7)
cardiovascular diseases	50 (53.7)	30 (58.8)	19 (52.7)	7 (41.1)
anaemia	34 (36.5)	15 (29.4)	10 (27.7)	6 (35.2)
iron deficiency	35 (37.6)	19 (37.2)	11 (30.5)	8 (47)
Vitamin B deficiency	5 (5.3)	3 (5.8)	3 (8.3)	3 (17.6)
diabetes	**14 (15)**	**19 (37.2)**	3 (8.3)	2 (11.7)
liver disorder	17 (18.2)	15 (29.4)	10 (27.7)	6 (35.2)
thyroiditis	6 (6.4)	6 (11.7)	2 (5.5)	2 (11.7)
thyroid function	26 (27.9)	12 (23.5)	7 (19.4)	3 (17.6)
desquamative gingivitis	14 (15)	11 (21.5)	3 (8.3)	5 (29.4)
lip involvement	3 (3.2)	5 (9.8)	2 (5.5)	0 (0)
autoimmune disease	17 (18.2)	10 (19)	6 (16.6)	5 (29.4)
allergy to dental materials	5 (5.3)	1 (1.9)	1 (2.7)	1 (5.8)
HPV present in lesion cells	24 (25.8)	18 (35.2)	12 (33.3)	7 (41.1)

Predisposing factors for OLP and OL (any risk model).

Regression analysis revealed (involving data of OLP and control patients' data) that out of the examined systemic factors some may work as a predisposing factor for OLP. HPV infection (p=0.00;

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Exp(B): 8.61), iron deficiency (p=0.00; Exp(B):6.07), diabetes (p=0.01; Exp(B): 5.2), and thyroid function disorders (p=0.01; Exp(B): 2.81) seem to behave as risk factors for OLP.

A bit different composition of systemic predisposing factors (involving OL and control patients' data) was found in case of OL: HPV infection (p=0.00; Exp(B): 12.29), iron deficiency (p=0.00, Exp(B): 5.53), and diabetes (p=0.013, Exp(B): 5.07).

3.2. Possible Predisposing Factors for Atrophic-Erosive OLP or Non-Homogenous OL (High Risk Model)

The main risk factor (all OLP subtypes" data) for erosive forms of OLP is diabetes (p=0.026; Exp(B): 2.93). While in case of non-homogenous OL no specific systemic risk factor was identified from the examined.

3.3. Lip Involvement

In OLP patients lip involvement seems to be affected by gender (p=0.014; Exp(B): 9.17), by smoking (p=0.003; Exp(B): 0.023), and diabetes (p=0.011; Exp(B): 9.89). In OL patients no systemic predisposing factor could have been detected amongst the examined factors.

3.4. Desquamative Gingivitis

In OLP thyroiditis provides the highest impact on desquamative gingivitis (p=0.00; Exp(B): 19.67). In OL there is no specific systemic factor amongst the investigated, which may influence this type of location.

3.5. Improvement of Co-Morbid Diseases and Lesions in OLP and OL Patients

One-hundred and ninety-seven patients (144 OLP +53 OL) were followed up for the average of 47.66 months (min-max: 1-203 months, SD: 54.19). On introduction to the study period in the OLP group there were 91 patients with non-atrophic-non-erosive lesions, while 53 had atrophic-erosive form. Amongst OL patients entering the study 38 patients were classified as having homogenous OL, while 15 patients were starting the study period with non-homogenous OLs.

By the end of the study, in terms of systemic conditions from all 197 patients (144 OLP and 53 OL) patients, 11 had not shown any improvement, while 82 had shown partial improvement, and 104 had full recovery. Seventy-nine OLP patients fully recovered from comorbid condition, 59 partially improved, and 6 had not improved at all. In case of OL patients 25 of them had shown full recovery, 23 had mild improvement, and the rest (n=5) had not improved at all from the systemic condition.

Parallel with this, lesions also regrediated to a better condition: in case of OLP in 38 patients the lesion clinically disappeared, in 106 patients the lesion was in a non-erosive-non-atrophic form (Table 4). In 5 patients with OLP there was no change, but these patients had non-erosive-non atrophic forms even at the beginning. In 1 female OLP patient the lesion fluctuated to non-erosive-non-atrophic to erosive-atrophic forms. She had Hashimoto thyreoditis with hypofunction. Never was a smoker, and she also neglected alcohol consumption. After nearly 17 years of follow up (in which her compliance was not fully satisfactory) there was a lymph node enlargement in the submandibular area, on the right side. Biopsy from OLP lesion had not even shown any dysplasia, just had shown histological characteristics of OLP but the lymph node biopsy confirmed OSCC origin. She had been referred to maxillofacial oncology.

There was another male patient who quit follow up after 3 years (at that point having non-atrophic-non erosive OLP form at small areas of tongue margin). Then after 5 years he was back with an erosive-atrophic lesion on the right side of the tongue. Biopsy confirmed an in situ carcinoma. He was also referred to maxillofacial oncology. After the tongue surgery the OLP disappeared from oral cavity. After 2 years OLP was coming back, so he had been under double control for years.

In case of OL 18 lesions disappeared (13 homogenous at the beginning, and 5 non-homogenous OL at the beginning). Thirty-five OL lesions were presented in a homogenous form by the end of the study period (Table 5). Comparison of lesion scores of OLP and OL patients, at the beginning (mean

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±SD: 1.34±0.47) and at the end of follow-up period (mean ±SD: 0.72±0.46) had shown significant difference (p=0.000). Improvement of lesions (OLP and OL), and improvement of systemic diseases correlated significantly: R=0.34, p=0.000.

Table 4. OLP lesions: number and types of lesions at the beginning and by the end.

	lesion not present by end point	non-atrophic/non-erosive OLP present by end point	atrophic-erosive OLP by the end	Total
non-erosive-non-atrophic OLP at the beginning	23	68	0	91
erosive-atrophic OLP at the beginning	15	38	0	53
Total	38	106	0	144

Table 5. OL lesions: number and types of lesions at the beginning and by the end.

	lesion not present by the end	homogenous OL present	non-homogenous OL by the end	Total
homogenous OL at the beginning	13	23	0	36
nom-homogenous OL at the beginning	5	12	0	16
Total	18	35	0	53

4. Discussion

In OLP and OL patients the frequency of CVD seemed higher than controls, but statistically it could not be proven [22]. Previous studies examined this relationship, though drugs taken for diseases e.g. hypertension may interfere with OLP, or in case of OL the common risk factor could be smoking [23]. Strangely there was no difference in the frequency of smokers, folic acid and vitamin B12 deficient patients, and the number of patients with thyroiditis, and autoimmune disease in each group. Earlier studies have not examined the prevalence of these conditions compared to subjects having healthy appearing oral mucosa.

Both OLP and OL patients harboured significantly higher HPV, and had a significantly higher number of patients with iron deficiency than controls. Having HPV in more lesions than in normal oral mucosa was shown earlier with the highest frequency in OL in other studies [19].

In OLP patients the diabetes and thyroid function disorders seem to occur in a higher prevalence, which emphasizes the importance of metabolic problems in OLP aetiology [24]. Both in diabetes types and OLP the presence of autoreactive cells was proven. Both CD4+ and CD8+ cells play a role in both aetiologies. In OLP in the histological picture mainly in the non-erosive-non atrophic variants the most T cells express CD8+. In a study it was shown that in erosive-atrophic variants in the histology the expression of CD4 + cells start to emerge besides CD8+ cells, mainly perivascularly [25]. The other possible connection between OLP and diabetes is that the main metabolic route of these CD4+ and CD8 + lymphocytes are through glycolysis and the pentose phosphate pathways. If sugar take-up of lymphocytes mainly T or B types disturbed, as it is in diabetes, their functions are not performed in the original way.

Though OL lies primarily on local risk factors but liver function problems increase the co-occurrence of infections and they also deteriorate iron metabolism, and thereby haemoglobin production. Liver diseases also increase the probability of secondary diabetes, and thyroid problems

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[26]. Liver function problems mainly toxic ones, also may have common etiological factor with leukoplakia: and that is alcohol [27].

HPV infection, iron deficiency, and diabetes seem to serve as risk factors for both OLP and OL formation. Thyroid function problems as they could also be related to diabetes, provide additional risk for OLP formation, but not for OL. The major risk factor for erosive OLP is diabetes. This is in accordance with previous studies [24].

Iron deficiency affects the functions of T regulator (Treg) cells and Natural Killer (NK) cells, while diabetes affects more the function of CD8+ and CD4+ cells (Th1 and Th2). Iron also takes part is the regeneration and proliferation of epithelial cells by taking part in haemoglobin formation, oxygen transport, and DNA synthesis, mitochondrial respiration, but also is an important element in oxidative stress and the elimination of inflammations. In this study in case of OL no certain factor was identified from the examined that has a profound responsibility for the erosiveness of the lesion. Probably in this pool of patients with HPV infections, there were no predisposing genes that help HPV multiplication. In case of the GCC haplotype of the interkeukin-10 gene promoter the clearance of high risk HPVs was reduced. Lower production of IL-10 may impair the production of anti-inflammatory cytokines that are needed for the proper elimination of HPVs by Th1-Th2 immunoregulation. Certain HLA-DR types can also be tied to the acquisition or elimination of HPVs. [28].

Other studies have not tried to answer the aetiology of lip involvement in OLP. Though the frequency of lip involvement is the same across both OLP and OL groups. In case of OLP the main effectors are gender, smoking, and diabetes. While gender and diabetes increases the possibility, until smoking seems to reduce the frequency. All of them may alter immune function of patients [29]. Smoking and diabetes can affect both regenerative abilities by reducing oxygen supply, and changing immune functions. Smoking seems to suppress all types of immunoreactions, while diabetes mostly alters T and B cell activities as mentioned before. Diabetes can also increase collagenase activity in tissues [30].

In case of OL from the examined characteristics none could be tied to OL lip involvement. In OL lip involvement is mainly devoted to sun exposure, not for systemic reasons, but smoking may have an augmenting effect[31].

Desquamative gingivitis seems to be a sign of thyroiditis in OLP patients. In Hashimoto thyroiditis the serum level of IL-2, Il-18, and IFNγ is higher in these patients. This is also true for OLP patients [32]. In Hashimoto the immune response seems to be characterized by Th1 pattern of cellular immunity. Certain gene polymorphisms serve as risk factors for OLP formation [32]. These are γ-interferon and tumour necrosis factor- α genes, both of which take part in the activation of Th1 cell route.

In case of OL none of the examined factors affect gingival location [33]. In OL it is more probable that gingival location is more adherent to plaque induced periodontal disease (gingivitis or periodontitis). Previous studies of OLP examined the prevalence of different thyroid diseases, primarily hypothyroidism, and autoantibodies produced in thyroiditis [34].

We could relate the improvement of OLP and OL lesions to comorbid diseases. The betterment of comorbid diseases in general did improve OL condition, but there were no specific diseases that had a major effect on OL lesions that were identified. The pathogenesis of OL lies more on local mucosa irritation to which chronic inflammation occurs secondary to local irritation.

For the first sight, the role of the comorbid diseases in healing does not seem to be important, but their effect in regeneration cannot be denied. Furthermore, iron and vitamin B deficiencies and overload are considered to be precancerous conditions that may promote tumour genesis [35–37]. Diabetes also possesses a risk for tumour formation by reduced regenerative abilities, and altered immunological reactions[38]. However as with many conditions, the treatment of diabetes largely depends on patient cooperation. Patients must be motivated enough to take the prescribed medications at the given times. Lifestyle and habit changes are also a major effectors of the treatment

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process. Diabetic patients are advised to make changes in their diet to control sugar intake and engage in regular exercise.

The aforementioned and evaluated therapy for OLP and OL lesions targets systemic diseases all of which by elevating inflammatory cytokines or lacking basic nutritional elements, like vitamins or macro-and microelements reduces the regenerative and protective potential of the oral mucosa [36,37]. Hyperkeratosis, atrophy, and erosion the basic histological phenomena of both OLP and OL lesions showing an increasing apoptotic rate, respectively [39][40]. Systemic diseases also provide the same effect on the lesions by augmenting the increase in their apoptotic rate. Conclusively, improvement of a systemic disease may reduce the cell death rate in lesions. Reduction of lesions to normal cell death rate, reduces the potential of cancer formation. Parallel the same effect is provided in case of cell senescence, where the oncogene induced senescence will be halted [41].

Earlier treatment options for OLP and OL were very limited and reduced to topical treatment. In this investigated population OLP lesions improved within 3-6 months, whereas OL lesions improved less rapidly, over 6 months. In the course of the previously mentioned local and systemic treatments however, leukoplakia changed their phenotype to homogeneous white lesions in each case, representing a lower risk for malignant transformation. Improvement was the most impressive in OLP patients with previously undiscovered or diagnosed but not optimally controlled coinciding systemic disorders, subsequent to the introduction of appropriate therapy. Overall, it was found that improvement of background systemic diseases has a positive effect on the regression of precancerous lesions.

As comorbid disease treatment was promoted for these patients in cooperation with physicians, other specialists, and home doctors we could increase the prevalence of lesion elimination compared to previous studies. Lesion check-up was repeatedly done by oral medicine specialist.

The same process was revealed in the pathogenesis of diabetes, and atherosclerosis, the latter disease belonging to cardiovascular diseases. In all the above mentioned diseases there is an increased Th1 activity over Th2. On one hand this step of the pathogenesis seems to be the common factor by which these diseases may promote each other [42]. On the other hand, atherosclerosis is related to hyperlipidaemia which beside diabetes belongs to metabolic syndrome. An association between erosive type OLP, diabetes mellitus and arterial hypertension was first reported by Grinspan in 1996 [43]. Earlier studies hypothesised that the association of erosive type OLP with diabetes and arterial hypertension could be attributable to iatrogenic effects of the drugs used for diabetes and hypertension treatment [44]. In case of atrophic-erosive OLP an additional effect may exist as these atrophic-erosive lesions possess increased rates of apoptosis, and altered senescence. On the one hand possibly because of increased rates of Th1 cell activity and on the other hand because of increased tissue collagenase activity[30].

In the pathogenesis of autoimmune conditions, an over activation of the Th2 cell population can occur. Hypothetically this event can counteract or augment the Th1 over activation, depending on the cytokine pattern. The Th1 and Th2 cells exist in close interaction [45]. Glucocorticoids do suppress the Th1 axis and there is a shift to Th2 mediated immunity, rather than a general immunosuppression. This is achieved by the inhibition of the production of Il-12, INFα, INFγ, and TNFα. Practically this is how acute and chronic stress can affect diseases formation [46].

In case of OL the betterment effect of comorbid disease improvement is mainly attributable to regaining regenerative abilities. The subepithelial lymphocyte infiltration, which in this case is mainly Th2, refers to presence of mechanical, chemical irritations (effects of smoking), infections, and stress.

Conclusion: Only local treatment does not give satisfactory results. Systemic approach or as previously said “holistic” approach would provide better results.

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