EVALUATION OF THE ROLE OF YKL-40 AND INTERLEUKIN-8 (IL-8) AS BIOMARKERS FOR MALIGNANT TRANSFORMATION IN ORAL LICHEN PLANUS

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ABSTRACT

Objective: This investigation was conducted to measure the levels of serum and salivary YKL-40 and IL-8 in patients suffering from OLP and OSCC to assess their potential role as biomarkers of oral cancer.

Methods: Forty five subjects with age ranging from 30 to 70 years were distributed into 3 groups; 15 patients having atrophic and/or erosive OLP, 15 patients suffering from OSCC and 15 systemically healthy control individuals. YKL-40 and IL-8 were identified in serum and saliva samples utilizing enzyme-linked immunosorbent assays.

Results: Serum YKL-40 and salivary levels of YKL-40 and IL-8 in patients with OSCC and OLP were significantly higher than the healthy control group. In order to differentiate patients having OLP from those suffering from OSCC, our study utilized the analysis of the receiver operating curve (ROC) which showed an AUC of 0.878, 0.789, 0.789 and 0.7 for serum YKL-40, salivary YKL-40, serum IL-8, and salivary IL-8, respectively. Serum YKL-40 had the highest diagnostic accuracy revealing 93% sensitivity and 73% specificity. That has been followed by salivary YKL-40 and serum IL-8, both revealing a good diagnostic accuracy with 93%, 80% sensitivity, and 60%, 73.3% specificity respectively. Salivary IL-8 as well yielded a good diagnostic accuracy and revealed degrees of sensitivity (80%) and specificity (63%). Cut off values of the biomarkers under investigation has been selected according to the distribution of sensitivities and specificities

Conclusion: YKL-40 and IL-8 might be counted as biomarkers for identifying cancerous changes of OLP and the initial stage of OSCC.

KEY WORDS: Oral lichen planus, Oral squamous cell carcinoma, YKL-40, IL-8. Serum, Saliva.

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INTRODUCTION

Oral lichen planus (OLP) is considered to be one of the autoimmune disorders which appears in several different clinical forms that occur separately or simultaneously in the form of plaque-like, reticular, bullous, erosive and atrophic lesions.\(^1\)

The possibility of cancerous changes in OLP is a debatable issue and is yet a matter of dispute in the current literature. OLP is counted as a premalignant condition according to the World Health Organization (WHO) and having a risk of malignant changes varying between 0% and 10%.\(^2\) Previous observations showed that regarding malignant transformation, there is no gender predilection with greater occurrence in individuals exceeding 40 years and most commonly occurring in the erosive type.\(^3\)

The most common of all malignancies of the head and neck is that affecting the oral cavity, with oral squamous cell carcinoma (OSCC) being by far the mostly frequent single entity and highly aggressive malignancies worldwide, accounting alone for about 90% of all oral cancers.\(^4\)

A scientific report strongly suggested that inflammation remains a crucial cause of specific malignancies of the epithelium.\(^5\) Increased conversion of normal cells to pre-neoplastic centers is associated with unresolved chronic inflammation which subsequently promotes cancer development.\(^6\) These inflammatory injuries lead to the up-regulation of inflammatory mediators like tumor necrosis factor α (TNFα), interferon α (IFN α), IL-1 α/β and IL-6,\(^7\) which consequently promotes the expression of pro-inflammatory chemokines.\(^8\)

One of the known pro-inflammatory chemokines is IL-8 which is released by a range of various cell types as neutrophils, lymphocytes, endothelial cells, epithelial cells, fibroblasts, monocytes, macrophages, as well as numerous cancer cells.\(^9, 10\)

IL-8 is a significant moderator of host reaction to inflammation and trauma,\(^11\) and takes part in the stimulation and attraction of neutrophils to the location of insult or infection.\(^12\) Moreover, it attracts T cells, natural killer cells, eosinophils and basophils.\(^13\) Therefore, IL-8 is considered to play an essential part in the natural immunity offering a primary line of resistance to attacking pathogens.\(^14\)

Healthy tissues have insignificant amounts of IL-8 but its concentration quickly reaches 10–100 times its baseline level in reaction to pro-inflammatory cytokines like TNF-α or IL-1β, bacteria or viruses, and cellular stress.\(^15\) Keratinocytes in OLP patients can synthesize IL-1 and TNF-α.\(^16\) Moreover, mononuclear cells in the peripheral blood as well as those infiltrated in the tissues in mucosal OLP patients, can produce TNF-α.\(^17\) Furthermore, following an increase in releasing of both IL-1 and TNF-α locally and systemically, macrophages, keratinocytes, endothelial cells, fibroblasts and T-cells in OLP lesions release significant amounts of IL-8, which leads to greater infiltration of T-cells such as cytotoxic T-cells locally in OLP. In addition, previous studies revealed that serum levels of IL-8 and IL-6 are greater in subjects having OLP in comparison to healthy individuals.\(^18, 19\) and that serum level of IL-8 is a more specific indicator of OLP than IL-6. This suggests that IL-8 could contribute to the pathologic process of OLP.\(^18\)

Elevated amounts of IL-8 might augment carcinogenesis by promoting DNA damage and proliferation of cells as well as by up-regulating the action of collagenase type IV and matrix metalloproteinase -2 (MMP -2).\(^20\) Enhanced collagenase activity promotes invasion of cancer cells, increased angiogenesis and subsequently metastasis. Moreover, the use of synthesized positive inotropic agent (vesnarinone) lead to the down regulation of IL-8 expression which consequently inhibited both angiogenesis and tumorigenicity of OSCC cells.\(^21\)
YKL-40, also named Chitinase-3-like-1 (CHI3L1)\(^2\) is a secreted glycoprotein, encoded by chitinase-3-like 1 protein.\(^2\) Several types of cells as endothelial cells, cartilage, inflammatory cells, and cancer cells secrete YKL-40.\(^3\) While the precise role of YKL-40 is unidentified, it has remained linked to several inflammatory and immune diseases in addition to numerous malignancies.\(^2\),\(^5\),\(^6\)

The amounts of YKL-40 are raised during inflammation, considering that it plays a significant part in chemotaxis and in the activation and recruitment of inflammatory cells, as it takes part in the process of differentiation, proliferation and apoptosis of cells, angiogenesis, and extracellular matrix remodeling.\(^2\),\(^5\),\(^6\)

Poor prognosis of a variety of medical, inflammatory and tumor processes are related to the increased amounts of YKL-40 in serum.\(^7\),\(^8\) Moreover, YKL-40 is considered to be one of the pro-inflammatory agents and has been described to promote the induction of chemokines as IL-8 from cancer cells.\(^9\),\(^10\)

Accordingly; this investigation was conducted to measure the levels of serum and salivary YKL-40 and IL-8 in patients suffering from OLP and OSCC to assess their potential role as biomarkers of oral cancer.

SUBJECTS AND METHODS

Forty five subjects with age ranging from 30 to 70 years were admitted in this investigation. They were enrolled from the outpatients’ clinic of Oral medicine and Periodontology department, Faculty of Dentistry, Cairo University. Subjects were distributed into 3 groups: 15 patients having atrophic and/or erosive OLP, 15 patients suffering from OSCC and 15 systemically healthy control individuals. For each individual, a thorough medical history was acquired based on the modified Cornell Medical Index’s questionnaire.\(^3\) An informed consent was signed by all participants once the nature of the investigation has been clarified.

Diagnosis of patients with OLP as well as OSCC was done clinically and biopsy specimens were obtained from the lesions to confirm the diagnosis histopathologically.

Collection of saliva samples:

Before any treatment and from all subjects, complete unstimulated saliva was assembled. For not less than one 60 minutes prior to sampling, all participants were requested to abstain from drinking, eating, or consuming chewing gum. Samples were acquired by requesting from the patient to swallow at first, incline the head frontward, and for 5 minutes, in the absence of swallowing, spit the whole saliva within 50-ml sterile centrifuge tubes. Once assembled, all specimens were directly kept at -20 °C until analyzed.

Serum sampling:

From each individual, 2 ml of venous blood samples were drained by regular venipuncture. In sterile tubes containing 15% K3EDTA solution, all blood sample were collected.

Detection of serum and salivary IL-8 samples:

Amounts of IL-8 were estimated in all salivary and serum samples by using an ELIZA kit (Orgenium laboratories, business unit, Finland). A sandwich-type ELIZA was adopted where a polyclonal anti-IL-8 antibody, adsorbed onto micro wells, binds IL-8 in the specimen. This assay utilize a human IL-8 specific antibody treated on a 96-well plate. Within the wells, samples, standards, and biotinylated anti-human IL-8 are pipetted and any IL-8 existing is bound via the immobilized antibody. HRP-conjugated streptavidin is pipetted into the wells once unbound biotinylated antibody is washed away. Again the wells are washed. A color comparative to the quantity of bound IL-8 develops after adding to the wells the TMB substrate solution. The color changes from blue to yellow by the Stop solution. Using ELIZA reader, the strength of the color is evaluated at 450 nm.
Evaluation of YKL-40 in serum and saliva:

Utilizing ELISA kit presented by Quantikine R & D systems, Minneapolis, USA (Catalog Number DC3L10), quantitation of Human YKL-40 in saliva and serum samples was performed. The quantitative sandwich enzyme immunoassay method was employed. Pre-coated onto a microplate, a monoclonal YKL-40 specific antibody has been used. After pipetting the samples and standards within the wells, any YKL-40 existing is held via the immobilized antibody. Once washed, an enzyme-linked polyclonal YKL-40 specific antibody is put into the wells. After adding to the wells a substrate solution, color appears proportional to the quantity of YKL-40 secured in the first stage. The concentration of the color is measured from the standard curve at 450nm using ELISA reader.

Statistical analysis

Quantitative data were demonstrated as median, mean, standard deviation (SD), range (Minimum – Maximum) and 95% confidence interval (95% CI) for the mean values. By inspecting the data distribution and by means of Kolmogorov-Smirnov and Shapiro-Wilk tests, data were investigated for normality. Age data revealed normal (parametric) distribution, while the data for YKL-40 and IL-8 revealed non-normal (non-parametric) distribution.

For parametric data; one-way ANOVA test was utilized to compare between the three groups. Whereas, Kruskal-Wallis test was utilized to compare between the three groups for non-parametric data. When Kruskal-Wallis test is significant, Dunn’s test was applied for pair-wise comparisons. Qualitative data were demonstrated as frequencies and percentages. To compare between the three groups Fisher’s Exact test was adopted. The significance level was set at $P \leq 0.05$.

A receiver operating characteristic (ROC) curve study was executed to evaluate the diagnostic efficacy of the biomarkers under study. A straight estimate of the diagnostic accuracy of the tested biomarkers was offered by the area under the curve (AUC). The biological marker which revealed the biggest AUC has been recognized as manifesting the greatest diagnostic accuracy for distinguishing OLP from OSCC. The value with the greatest sensitivity and specificity and which existed nearest to the upper left side of the curve determines the best cut off point for each biomarker. IBM® SPSS® Statistics Version 20 for Windows was utilized to perform the statistical analysis.

RESULTS

In serum, OSCC group revealed the statistically significant highest mean YKL-40 level. OLP group showed a significantly lower mean value. The control group revealed the statistically significantly lowest mean YKL-40 levels. A significant difference between OSCC group and OLP group also between each of the study groups and the control group was shown.

Similarly, in saliva, OSCC group also yielded the statistically significantly highest mean YKL-40 level. OLP group showed a lower mean value followed by the control group showing the lowest mean value. No significant difference between OSCC and OLP groups was detected, yet upon comparing both the OSCC group and the OLP group to the healthy controls, a significant difference was shown.

As regards IL-8, in serum, a statistically significant difference among OSCC group and the control group was shown being highest in the OSCC group. Whereas, between OSCC and OLP or between OLP and control, no significant difference was detected.

In saliva, no significant difference was shown comparing OSCC group to OLP group; both

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revealed the significantly highest mean levels of IL-8. Meanwhile, the statistically significantly lowest mean IL-8 level was shown by control group.

A ROC curve analysis was conducted to distinguish the studied biomarkers for the initial prediction of OSCC. For identifying the initial stage of OSCC, cut off values of the biomarkers under investigation has been selected according to the distribution of sensitivities and specificities.

In order to differentiate patients having OLP from those suffering from OSCC, analysis of the ROC curve showed an AUC of 0.878, 0.789, 0.789 and 0.7 for serum YKL-40, salivary YKL-40, serum IL-8, and salivary IL-8, respectively, (Fig.1). Serum YKL-40 had the highest diagnostic accuracy (AUC 0.878), where a cutoff point of >1771.9 ng/ml has been identified revealing 93 % sensitivity and 73 % specificity. That has been followed by salivary YKL-40 and serum IL-8, both revealing a good diagnostic accuracy (AUC 0.789), with 93%, 80 % sensitivity, and 60%, 73.3 % specificity respectively with a cut off values of >1095.575 and >9.32 pg/ml respectively. Salivary IL-8 as well yielded a good diagnostic accuracy (AUC 0.7) with a cut-off point of >2980 pg/ml and revealed degrees of sensitivity (80%) and specificity (63%). The subjects exceeding such cut off measures has been regarded as cancerous and beneath such cut off points has been regarded as patients having OLP alone.

Table 3 shows the cut-off points, corresponding sensitivities and specificities as well as the AUC for the biomarkers under study in diagnosing OSCC, OLP and differentiating between them.

| Table 1: Descriptive statistics and results of Kruskal-Wallis test for comparison between YKL-40 levels (ng/ml) in the three groups |
|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|
|                      | Group               | Mean                | SD                  | Median               | Minimum             | Maximum              | 95% CI               | P-value              |
|                      |                     |                     |                     |                     |                     |                     |                     |                     |                     |
| Serum               | OSCC                | 5141.8              | 4900.7              | 4399.1              | 1272.6              | 22534.0              | 2378.1              | 7905.6              | <0.001*              |
|                     | LP                  | 2602.7              | 1640.3              | 2094.6              | 769.2               | 4989.4               | 1694.3              | 3511.0              |                     |
|                     | Control             | 965.5               | 237.0               | 924.8               | 555.8               | 1551.2               | 974.6               | 1096.8              |                     |
| Saliva              | OSCC                | 1718.0              | 1170.5              | 1237.5              | 1012.2              | 5678.0               | 1069.8              | 2366.2              | <0.001*              |
|                     | LP                  | 1107.6              | 240.1               | 1219.5              | 561.8               | 1310.4               | 466.8               | 1240.6              |                     |
|                     | Control             | 752.2               | 296.3               | 723.1               | 211.8               | 1239.7               | 588.1               | 916.4               |                     |

*: Significant at P ≤ 0.05, dissimilar letters in the same column indicate statistically significant difference

| Table 2: Descriptive statistics and results of Kruskal-Wallis test for comparison between IL-8 levels (pg/ml) in the three groups |
|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|
|                      | Group               | Mean                | SD                  | Median               | Minimum             | Maximum              | 95% CI               | P-value              |
|                      |                     |                     |                     |                     |                     |                     |                     |                     |                     |
| Serum               | OSCC                | 29.2                | 32.7                | 20.4                | 3.2                 | 108.7               | 11.1                | 47.3                | 0.003                |
|                     | LP                  | 20.2                | 28.1                | 11.1                | 2.0                 | 91.0                | 4.6                 | 35.7                |                     |
|                     | Control             | 6.0                 | 2.5                 | 6.2                 | 2.5                 | 9.2                 | 4.6                 | 7.4                 |                     |
| Saliva              | OSCC                | 2840.9              | 1350.1              | 3137.0              | 258.0               | 4874.0              | 2093.3              | 3588.6              | <0.001*              |
|                     | LP                  | 3008.9              | 387.8               | 3140.4              | 2063.1              | 3301.0              | 2794.2              | 3223.6              |                     |
|                     | Control             | 434.4               | 117.3               | 381.7               | 270.4               | 641.8               | 369.4               | 499.3               |                     |

*: Significant at P ≤ 0.05, dissimilar letters in the same column indicate statistically significant difference
Currently, OSCC is detected based on detailed clinical examination joined with laboratory investigation through biopsy acquisition for histological testing. Unfortunately, most of the cases of OSCC are not identified except after an advanced stage of the cancer has been reached; thus, early cancer detection using a reliable diagnostic marker is needed to reach the best prognosis and also raise the possibility of treatment.  

Based on the current literature, the authors’ claim that this is the primary investigation that aims to study the level of YKL-40 in the saliva of patients with OSCC and OLP. In this study, YKL-40 in serum and saliva was significantly higher in patients suffering from OSCC and OLP as compared to healthy individuals being highest in OSCC group. Also, IL-8 in serum and saliva was significantly higher in OSCC and OLP groups when compared to the healthy individuals.

It has been indicated that chronic inflammation

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Cut off point</th>
<th>Sensitivity %</th>
<th>Specificity %</th>
<th>AUC (95% CI)</th>
<th>SE</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum YKL-40 (ng/ml)</td>
<td>1771.9</td>
<td>93.3</td>
<td>73.3</td>
<td>0.878 (0.78-0.975)</td>
<td>0.05</td>
<td>&lt; 0.001</td>
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<td>Salivary YKL-40 (ng/ml)</td>
<td>1095.575</td>
<td>93.3</td>
<td>60</td>
<td>0.789 (0.658-0.92)</td>
<td>0.067</td>
<td>0.002</td>
</tr>
<tr>
<td>Serum IL-8 (pg/ml)</td>
<td>9.32</td>
<td>80</td>
<td>73.3</td>
<td>0.789 (0.649-0.929)</td>
<td>0.071</td>
<td>0.002</td>
</tr>
<tr>
<td>Salivary IL-8 (pg/ml)</td>
<td>2980.2</td>
<td>80</td>
<td>63.3</td>
<td>0.7 (0.532-0.868)</td>
<td>0.086</td>
<td>0.03</td>
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**DISCUSSION**

Currently, OSCC is detected based on detailed clinical examination joined with laboratory investigation through biopsy acquisition for histological testing. Unfortunately, most of the cases of OSCC are not identified except after an advanced stage of the cancer has been reached; thus, early cancer detection using a reliable diagnostic marker is needed to reach the best prognosis and also raise the possibility of treatment. Based on the current literature, the authors’ claim that this is the primary investigation that aims to study the level of YKL-40 in the saliva of patients with OSCC and OLP. In this study, YKL-40 in serum and saliva was significantly higher in patients suffering from OSCC and OLP as compared to healthy individuals being highest in OSCC group. Also, IL-8 in serum and saliva was significantly higher in OSCC and OLP groups when compared to the healthy individuals.

It has been indicated that chronic inflammation
supports cell proliferation, differentiation, survival and growth, through the production of different cytokines. This can promote initiation and progression of cancer. Accordingly, several trials have been adopted to recognize patients with OLP who were at risk of malignant transformation and it has been recommended that these patients should be cautiously followed and accurate diagnosis should be reached as early as possible.

Several studies demonstrated an increase in NF-kB dependent cytokines, IL-6, TNF-α, IL-1α and IL-8 in the various fluids of the oral cavity, serum, oral epithelial cells as well as tissue infiltrated mononuclear cells of OLP. Those investigations emphasize the probability that the NF-kB and its dependent cytokines create an inflammatory microenvironment which favors the beginning and/or progression of the cancerous alteration of OLP. The change in the expression level of proteins associated with cell proliferation rate and apoptosis can be utilized as a predictor for the increased possibility of malignant development.

Waugh and Wilson proposed that within the tumor microenvironment, IL-8 might act as an important modulating agent as its elevated expression has been represented in malignant cells and cancer associated macrophages. Additionally, Rao et al. confirmed that IL-8 activates other genes associated with cancer development such as that of vascular endothelial growth factor (VEGF), suggesting that it can contribute to cancer. It has also been reported to take part in tumor-derived angiogenic activity in various human cancers. Such findings intensely propose that IL-8 plays a role as a significant regulator in OSCC.

In the present study, and in all the included groups, salivary IL-8 levels were greater than that in the serum samples. These results aligned with previous investigations. Furthermore, serum IL-8 was shown to be higher in OSCC group with a highly significant difference when compared to the healthy controls. That was in accordance with previous studies which firmly showed a significantly elevated IL-8 levels in serum among subjects having OSCC than control subjects.

Comparing OSCC and OLP groups, this study showed no significant difference in IL-8 levels in saliva, while there was a highly significant difference when comparing each one of the groups to the control group. This was in agreement with former investigations comparing OSCC alone with the healthy control subjects. And, Zhang et al. who reported similar results comparing OLP, as one of the premalignant lesions, to healthy control subjects. However, other studies found highly elevated levels of IL-8 in saliva of OSCC group than oral premalignant and control groups which might be related to the dissimilarity in population and the different number of subjects included in those investigations.

The results of the current investigation advocate that the level of salivary IL-8 may demonstrate the possibility of malignant development in OLP and it may serve as an indicator of diagnosis and/or prognosis of the malignant change of OLP to cancer.

It has been shown that levels of YKL-40 in serum were increased in various diseases associated with chronic inflammation, suggesting its pathologic function is related to the process of extracellular matrix remodeling. This brought attention to the function of YKL-40 in the generation of a variety of human malignancies. For example, YKL-40 expression levels were significantly elevated in ovarian, brain, and breast cancer tissues than levels expressed in nearby normal tissues based on the gene microarray analyses. Moreover, a lot of clinical studies have proposed that metastasis and poor prognosis in several human malignancies, such as ovarian, colorectal, breast, brain cancer and leukemia was related to high serum levels of YKL-40 indicating that YKL-40 levels in the serum might act as a novel biomarker for human malignancies.
The present investigation observed that levels of YKL-40 in the serum was significantly higher in subjects suffering from OSCC compared to both, the OLP group and the healthy controls, this is in accordance with previous reports of an association between elevated levels of YKL-40 in serum and short survival rate in a variety of human cancers. Also salivary YKL-40 levels in saliva were higher than that in the serum in all groups. Salivary YKL-40 showed the highest levels in OSCC and OLP with no significant difference between them and both showed a significant difference while compared to the healthy control subjects.

The role of YKL-40 in malignancy and the tools by which it reveals cancer aggression are not fully recognized. It was proposed that YKL-40 may take part in cancer cells’ differentiation and proliferation, in their protection against apoptosis, in triggering angiogenesis and in tissue remodeling disruption. However, it has not been elucidated yet which cellular receptors are involved in mediating these effects.

Studies which suggest that YKL-40 might stimulate angiogenesis beside simultaneous elevations in IL-8, could indicate a link between YKL-40-induced IL-8 activity and angiogenesis. For instance, Kawada et al. 2012, indicated that YKL-40 induced IL-8 production from colon cancer cells promoted angiogenesis as well as macrophage recruitment. Therefore, YKL-40 appears to have an additional angiogenic action that is independent of VEGF. In addition Chen et al. indicated that YKL-40 can also activate the NF-κB pathway. Moreover, Shao et al. established that recombinant YKL-40 has a direct influence on angiogenesis. However, there is a deficiency in investigations linking between YKL-40 and IL-8 in both saliva and serum in the current literature, thus more studies are required to explain the exact function of YKL-40 in IL-8 generated angiogenesis and if the elevated YKL-40 noted in the current investigation could modulate angiogenesis in OSCC by elevating IL-8 levels.

Guerra et al. in a systematic review, established a conclusion that not many saliva biomarkers used for the initial discovery of oral malignancies were precise. The perfect diagnostic biomarker should be present in all patients with the disease, should show high sensitivity and specificity to disease, and should elicit a cut off point with negligible intersection between illness and normal conditions.

In the present study, in order to discriminate between patients suffering from OSCC and patients having OLP alone, the ROC curve interpretation for serum YKL-40 revealed that the AUC is 0.878 showing high sensitivity (93%) and specificity (80%) levels. This was followed by saliva YKL-40 and serum IL-8 both revealing a good diagnostic accuracy showing an AUC of 0.789 for both with sensitivity (93 % and 80%) and specificity (73.3% and 60 %) respectively. Salivary IL-8 also showed a good diagnostic accuracy (AUC 0.7) with levels of sensitivity 80% and specificity 63%. This investigation proposes that the studied biomarkers might serve as diagnostic indicators of malignant change of OLP into OSCC. This is in accordance with other reports showing that the initial angiogenic activity might participate in stimulating cancer development within dysplastic changes of the epithelium.

Thus, based on our work we can advocate that salivary YKL-40 and IL-8 could be counted as biomarkers for identifying cancerous changes of OLP and the initial stage of OSCC. The current study offers salivary biomarkers that are sensitive and might be used as a potential non-invasive way for the initial recognition of OSCC. However, further large-scale investigations needs to be conducted to determine the efficacy of these biomarkers as the identification of initial malignant transformation could be valuable for prompt intervention and a better chance of cure.
REFERENCES


