



CLINICAL DATA ANALYSIS ON THE ASSOCIATION BETWEEN PERIODONTAL DISEASE, THE DEVELOPMENT OF ORAL SQUAMOUS CELL CARCINOMA AND ORAL POTENTIALLY MALIGNANT DISORDERS

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SUMMARY:

Oral cancer is an aggressive disease characterized by low average survival rates.

Purpose: To examine the periodontal status in cases of primary oral squamous cell carcinoma (OSCC), oral potentially malignant disorders (OPMD), periodontitis, and healthy individuals in relation to its impact on the development of OSCC and OPMD.

Materials/Methods: The study involved 107 individuals with an average age of 54.22±14.38 years (58.9% male, 41.1% female), divided into four groups: Group I – patients with OSCC (n=43); Group II – patients with OPMD (n=21); Group III – patients with periodontitis (n=21); Group IV – healthy individuals (n=22).

Results: In the OSCC, OPMD, and periodontitis groups, a significantly lower mean number of existing teeth was observed (16.97, 18, and 22.8, respectively) compared to the healthy group (28.77), along with a tendency for a higher number of missing teeth in OSCC patients compared to those with periodontitis. We found significantly higher values of BOP (Bleeding on Probing) in OSCC patients (67%) compared to those with periodontitis (48.57%) and healthy individuals (9.65%). We consider BOP a potential risk indicator for oral cancer.

Conclusions: The trend toward a higher frequency of missing teeth in OSCC patients compared to those with periodontitis is associated with prior infection and inflammation in the oral cavity, which is suspected to play a role in oncogenesis. The significantly higher BOP values in OSCC patients compared to those with periodontitis indicate the influence of inflammation on the development of malignant processes. Periodontal treatment may be an effective approach to reducing the risk of carcinogenesis.

Keywords: oral squamous cell carcinoma, oral potentially malignant disorders, periodontitis, tooth loss, bleeding on probing,

INTRODUCTION:

Oral squamous cell carcinoma (OSCC) is the most common tumor of the oral cavity, with an increasing incidence worldwide, with up to 370,000 new cases per year [1].

OSCC is an aggressive disease characterized by a low median survival rate [2]. Thanks to the introduction of new techniques, the prognosis of cancer patients has improved significantly, however, the results are still not satisfactory due to lack of precise diagnosis. Treatment could be considered optimal if an adequate prognosis can be made. Therefore, accurate early cancer diagnosis and prognosis are essential to increase patient survival.

Oral cancer is etiologically engaged to various risk factors reported (i.e. smoking, alcohol use, chronic inflammation, ultraviolet (UV) radiation (for lip cancer), human papillomavirus (HPV) or Candida infections, immunosuppression, genetic predisposition, and diet) [3]. Inflammatory disease is suggested to be associated with the development of oral cavity cancer due to the involvement of several molecular pathways (inflammation related molecular pathways) [3].

Periodontitis has been defined as a chronic multifactorial inflammatory disease associated with plaque accumulation and progressive destruction of the tooth supporting apparatus [4]. The main features of periodontitis disease include the destruction of supporting tissues of the tooth manifested by clinical loss of attachment and radiographically assessed loss of alveolar bone, presence of periodontal pockets and bleeding from the gingiva. A large number of studies link periodontitis to systemic diseases, such as cardiovascular, type 2 diabetes, pulmonary disorders, pregnancy complications, rheumatoid arthritis [5]. Periodontal disease has been identified as an inde-

pendent marker and putative risk factor for head and neck carcinomas [6]. A meta-analysis performed on studies that used objective measures of periodontal disease demonstrated a significant association between periodontal disease and head and neck cancer. [6]. A systematic review reports a correlation between periodontal disease, oral carcinoma and oral potentially malignant disorders (OPMD) based on increased values of clinical attachment level (CAL), plaque index (PI), bleeding on probing (BoP) and radiographic bone loss in patients with OSCC and OPMD in most studies considered. [7] The establishment of a causal relationship between periodontitis and oral carcinoma may identify periodontal diseases as an independent risk factor for oral carcinoma and justify the need for their treatment to achieve a lower incidence and higher cancer patient survival rates. It is suggested that patients with periodontitis should be strictly monitored due to the increased risk of oral carcinoma or OPMD [7].

The interaction between the host cells and the oral microbiome in chronic periodontal disease and the wide range of cytokines, chemokines, matrix metalloproteinases (MMPs) and oxygen radicals are promoting cancer growth and progression. A strong link between periodontitis and oral cancer is suggested, with periodontal infection and the underlying chronic inflammation in both diseases being the main etiologic factor.

Aim:

To investigate periodontal status in patients diagnosed with OSCC, OPMD, periodontitis and healthy individuals in relation to the influence of periodontal disease on the development of oral cancer and precancer.

MATERIALS AND METHODS:

One hundred and seven patients with a mean age of 54.22 ± 14.38 years participated in the present study. The individuals were divided into the following two groups: 63 (58.9%) males and 44 (41.1%) females.

Clinical examination and thorough assessment of the periodontal status were performed in all individuals in order to reveal the following parameters: distribution of bleeding on probing in the mouth in percent (BOP), pocket depth (PD) and patient maximum probing periodontal pocket depth (PDmax), clinical attachment loss (CAL) and patient maximum clinical attachment loss (CALmax). Unstimulated whole saliva in an amount of 2 ml was collected according to the method described by Navazesh [8] and modified according to the method of Henson & Wong [9]. The samples were then transported to the laboratory and were centrifuged at 2600xg for 15 min at 4°C. The supernatant was transferred in a cryo-tube containing a solution of lyophilized protease inhibitor (SigmaFast Protease inhibitor, Sigma-Aldrich Co, St. Louis, MO, USA) – 1 µL of the protease inhibitor for each mL of

saliva. All samples were stored at a temperature of -80°C until the time of analysis. For simultaneous detection and quantification of cytokines and immunoregulatory molecules: BDNF; IL-6; IL-8; IL-1063; IL-15; IL-1RA; LIF; TNF-α was measured using the Myokine 8-Plex Human ProcartaPlex™ Panel (Thermo Fisher Scientific) by the multiplex assay method (ProcartaPlex™ Multiplex Immunoassay) based on magnetosphere technology (licensed from Luminex™).

The study participants were divided into 4 clinical groups: Group I – individuals with primary oral squamous cell carcinoma (OSCC) (n=43); Group II - individuals with OPMD - leukoplakia, erythroplakia, oral lichen planus (n=21); Group III – individuals with periodontitis (n=21); IV group – healthy individuals (n=22).

Statistical analysis: We used the Shapiro-Wilk test to assess the normality of the data distribution in the relatively small sample of the study. The Kolmogorov-Smirnov test is used in statistical analysis to examine data correspondence with a particular distribution. We used a non-parametric Mann-Whitney test to analyze a relatively small sample when the distribution is not normal, and the grouping variable has two categories.

RESULTS:

In the present study, the distribution of patients by gender in the groups is as follows: in the OSCC group – 65% are men and 35% are women, and in the OPMD group – 57% are men and 43% are women, in the periodontitis group - 65 % are men and 35% are women, in the group of healthy individuals – 41% are men and 59% are women.

Oral carcinoma is most prevalent in the 60-70 age group. OPMD is most prevalent in the 50-60 age group. Periodontitis is most prevalent in the 40-50 age group.

The average age in the OSCC group is 58.77 ± 12.74 , in the OPMD group – 56.19 ± 13.42 , in the periodontitis group – 55.81 ± 13.11 , and in the healthy group – 41.95 ± 13.35 .

The distribution according to the stage of periodontitis among the patients of group III is as follows: in stage I are 19% of cases, in stage II are 19% of cases, in stage III are 19% of cases, in stage IV are 43% of cases, as a large number of cases have severe periodontitis (stage III and IV), a total of 62%.

The examination of the dental status and the number of teeth present in the mouth shows the following: In group I, the average number of teeth present in the mouth is 16.97; for group II, the average number of teeth present in the mouth is 18; for group III the mean number of teeth present in the mouth is 22.81 and for the group of healthy individuals the number of teeth is 28.77. The comparative analysis found that there was a significant difference in the mean number of teeth present in the mouth between groups I and IV ($p < 0.001$);

there is a significant difference in the average number of teeth present in the mouth between II and IV groups ($p<0.001$); there was a significant difference in the mean number of teeth present in the mouth between group III and group IV ($p<0.001$). No significant difference was found in the average number of teeth present in the mouth between patients of I and II groups ($p=0.11$); between patients of II and III groups ($p>0.05$). There was no significant difference in the mean number of teeth present in the mouth between groups I and III, although there was a tendency for a greater number of missing teeth in patients with OSCC compared to those with periodontitis ($p=0.066$).

Regarding the periodontal status, the patients of group I are divided into individuals diagnosed with periodontitis – 69.8%, individuals without clinical evidence for periodontitis – 9.3% and completely edentulous individuals – 20.9%. In group I, a total of 90.7% of patients with periodontitis and complete edentulism were present. In the patients of group II, the cases with periodontitis are 73%, without periodontitis are 17.5%, and completely edentulous are 9.5%. In group II, the total number of patients with periodontitis and those with complete edentulism was 82.5%. In III, there were no patients with complete edentulousness, and all had attachment loss. In group IV, patients have no edentulousness and no attachment loss.

Regarding probing depth, the following mean values (PD) for the groups are reported: for group I – 2.05 mm, for group II – 2.09 mm, for group III – 3.36 mm and for group IV – 2.06 mm. A significant difference was found between mean PD values between group I and group III ($p<0.001$), as well as between group II and group III ($p<0.001$). No significant difference was found between PD values between the I and II groups ($p=0.71$).

The maximum probing depth values (PDmax) in the groups are, respectively: for I group – 3.5 mm, for II group – 3.44 mm; for group III, it is 4.08 mm and for group IV, it is 2.06 mm. The maximum values of probing depth (PDmax) in group IV was significantly lower compared to all other groups ($p<0.001$). PDmax in groups I and II did not differ significantly ($p=0.1$). There were no significant differences between PDmax values for

groups II and III ($p=0.96$) and between PDmax values for groups I and III ($p=0.97$).

CAL was reported as the main indicator for the severity of the periodontal disease. The results show that the existence of CAL was similar in patients with OSCC (85.3%) and those with OPMD (84.22%). The mean CAL for the oral carcinoma group was 1.86 mm; for the OPMD group, it was 1.61 mm; for the periodontitis group, it was 3.2 mm; and for group IV, it was unavailable.. Significant differences were found between CAL values for groups I and III ($p<0.001$), as well as between CAL values for II and III ($p<0.001$). There were no significant differences between CAL values for groups I and II ($p=0.26$).

We reported the maximum values of attachment loss CALmax in the studied groups. The maximum values of attachment loss (CALmax) in the OSCC group was 3.88 mm, in the OPMD group, it was 3.67 mm, and in the periodontitis group – 5.19 mm. A significant difference was found between CALmax values for groups II and III ($p=0.003$) and for groups I and III ($p=0.019$). When comparing CALmax values between the I and II groups, there is no significant difference ($p=0.23$).

Mean values of BOP showed some differences between the studied groups. For the OSCC group, the mean BOP was 67%, for the OPMD group, the mean BOP was 55.58%, for the periodontitis group, the mean BOP was 48.57% and for the healthy group, the BOP was 9.65%. There is a significant difference between BOP in groups IV and III ($p=0.005$), in groups IV and II ($p<0.001$) and in groups IV and I ($p<0.001$). There is a significant difference in BOP between groups I and III ($p=0.010$). There was a tendency for higher BOP values in the OSCC group compared to OPMD, but not significant ($p=0.053$). No significant differences were found between BOP values for groups II and III ($p=0.239$).

From the correlation analysis, it was found that the periodontal indicators “BOP”, “PD”, “PDmax”, “CAL”, and “CALmax” were positively correlated with age ($p<0.001$), and the indicator “present teeth” was negatively correlated with age ($p<0.001$). Mann-Whitney test was used for statistical data processing.

Regarding the prevalence of the risk factor of smoking, the within-group distribution is shown in Table 1.

Table 1. Distribution of patients according to the smoking factor in the clinical groups.

Smoking	Group I	Group II	Group III	Group IV
Non-smokers	13.90%	14.28%	33.33%	59.09%
Former smokers	16.27%	33.33%	14.28%	9.09%
Smokers up to 20 cigarettes	60.46%	42.85%	23.80%	27.27%
Smokers over 20 cigarettes	9.30%	9.50%	28.57%	4.54%
Total	100%	100%	100%	100%

The comparative analysis found that the percentage of non-smokers was significantly greater in the group of healthy individuals compared to those in the OSCC ($p<0.05$), OPMD ($p<0.05$), and periodontitis ($p<0.05$) groups. The relative proportion of current smokers smoking up to and over 20 cigarettes per day was statistically significantly greater in the OSCC group (69.76%) compared to healthy individuals (31.81%) ($p<0.05$).

DISCUSSION:

In recent years, the incidence of oral carcinoma has increased significantly. Ninety percent of oral cancer cases are histologically diagnosed as oral squamous cell carcinomas (OSCC). Despite new management strategies, the 5-year survival rate for oral cancer is still below 50% in most countries [3]. This low survival rate is mainly due to late diagnosis, as most cases of oral carcinoma are detected at an advanced stage (III and IV). Therefore, early diagnosis and treatment are essential to improve survival rates and quality of life in patients with oral carcinoma. Diseases of the oral mucosa, such as oral leukoplakia or oral lichen planus, which have a propensity for malignant transformation, need to be monitored, and the lesion must be removed before it becomes invasive.

The gender ratio of patients with the diagnoses under consideration shows unequal prevalence. Data from the literature indicate a more frequent development of oral carcinoma in men compared to women. The reported frequencies for the gender distribution in patients with oral squamous cell carcinoma are 57.2% for men and 42.8% for women [10] and 69.8% for men, and 30.2% for women [11]. According to a review of epidemiological data, the standard incidence of oral cancer worldwide is 4 per 100,000 (in men vs women, 5.5 and 2.5 per 100,000, respectively) [12]. In the present study, a similar frequency distribution by gender was found in the OSCC group – 65% for men and 35% for women. For the prevalence of OPMD in both genders, our results again show a higher percentage of males (57%) compared to females (43%) and are similar to the ratios reported in the literature, 59.99% of males and 39.89% of women among patients with OPMD [13].

Regarding the age prevalence of OSCC, the highest prevalence was reported in the 60-74 age group (41.1%) [10] and from the 4th to the 6th decade of life [11]. According to studies, in individuals over 50 years of age, the prevalence of OPMD is the most common [13].

The overall prevalence of periodontitis, as defined by the Centers for Disease Control and Prevention of the American Academy of Periodontology (including mild, moderate, and severe forms of periodontitis), is approximately 46% among persons 30 years of age and older. The prevalence of periodontitis increased from 24.8% among persons aged 30–34 years to 68.0% among persons 65 years and older [14]. In the present study, for the group of periodontitis, the prevalence of the disease was highest in the age group of 40-50 years, and the average age of persons

with periodontitis was 55.81 ± 13.11 . A strong negative correlation between the number of teeth present and age and a positive correlation between the periodontal parameters “BOP”, “PD”, “PDmax”, “CAL”, and “CALmax” and age found in the group of patients with periodontitis, confirms the age as a risk factor for periodontitis.

In our study, the OSCC and OPMD groups showed a prevalence of periodontitis (69.8% and 73%, respectively), which is consistent with the results of previous studies on the prevalence of periodontitis among patients with oral carcinoma – 76.9% [15]. We associate the high prevalence of periodontitis among the examined patients with OSCC and OPMD with the influence of infection and chronic inflammation in periodontitis on the development of oral pre-malignant and malignant disorders.

Our research showed that the OSCC, OPMD and periodontitis groups had a significantly lower mean number of available teeth (16.97; 18 and 22.8, respectively) compared to the healthy group (28.77). These results, together with the fact that the percentage of completely edentulous patients was the highest in the OSCC group compared to edentulous in the other groups, although without a significant difference, are consistent with the data of other authors, according to which the number of completely edentulous patients was larger in the group with oral cancer compared to the control group – no oral cancer [16]. It is known that tooth loss can be due to complications of caries and tooth fractures, but one of the main causes of tooth loss is periodontitis. We attribute the trend toward a higher incidence of missing teeth in patients with OSCC compared to those with periodontitis to antecedent infection and inflammation in conditions with decayed teeth and severe periodontitis, which have been suggested to play a role in oncogenesis.

Comparatively worse periodontal status has been reported in patients with oral cavity carcinoma. A higher number of missing teeth, complete edentulousness, significantly higher values of PD, CAL and BOP have been reported in patients with oral cancer compared to individuals without oral cancer [16]. According to another study, severe chronic periodontitis was prevalent in 88.6% of the group of patients with oral and oropharyngeal carcinoma and 32.5% in the control group (without carcinoma), with a significant difference between the values. Mean PD and CAL values were significantly higher for the oral carcinoma case group compared to the non-carcinoma control group. Comparison of periodontal indicators showed that the extent and severity of chronic periodontitis remained risk indicators for oral and/or oropharyngeal carcinoma even after adjustments for traditional confounders, i.e. smoking and alcohol consumption [17].

The following parameters are indicative of periodontitis severity: CAL, which reflects destruction, and PD, which reflects destruction and inflammation in periodontal tissues. Regarding the periodontal parameters – PD, PDmax, CAL, CALmax, we found a similarity between the

values for the OSCC and OPMD groups. The significantly higher values of CAL, CALmax and PD found by us in the periodontitis patients compared to the patients with teeth from the group of OSCC and OPMD shows that the severity of periodontitis is not decisive for the occurrence and development of OPMD and OSCC. In our opinion, periodontitis is a disease that, in most cases, persists for a long time and develops slowly, with periods of varying activity. The severity of periodontitis accumulates over time and is not directly related to the development of a malignant lesion. Although periodontitis severity indicators were not higher in the groups with premalignant and malignant lesions, periodontitis was not excluded as a risk factor for them.

Bleeding on probing is an indicator of inflammation in the periodontal tissues. In our study, we found significantly higher prevalence values of BOP in patients with OSCC (67%) compared to those with periodontitis (48.57%) and healthy subjects (9.65%) and a trend for a significant difference with the OPMD group (55.58%). These results point to the determination of BOP as a potential risk indicator for oral cancer. According to other authors, similar mean values of BOP were found in patients with and without oral/oropharyngeal carcinoma, 25.9% and 18.6%, respectively, without a statistically significant difference [17]. There are data on BOP of 46% and 35%, respectively, in patients with and without leukoplakia, providing evidence that BOP is associated with the occurrence of leukoplakia in a dose-dependent manner and that this association is independent of smoking [18].

BOP is one of the clinical signs of periodontitis activity. BOP is a widely used criterion for the diagnosis of inflammation of periodontal tissues. Sensitivity and predictiveness studies show that BOP is a limited but useful prognostic indicator in clinical diagnosis for patients in the periodontal maintenance phase. BoP has been shown to be the preferred diagnostic clinical test for documenting an inflammatory process at the bottom of the pocket of the dento-gingival or implantomucosa unit. It is important for clinical practice that BOP is a reversible inflammatory parameter that can be influenced by medical procedures, i.e. oral hygiene and biofilm removal [19].

We associate the high prevalence of BOP in OSCC with higher inflammation activity, which is probably the result of an increase in immunoregulatory molecules involved in intercellular interactions. It is likely that the widespread prevalence of periodontal inflammation causes a higher risk for the development of OSCC. This is a hypothesis repeatedly discussed in the literature. Chronic inflammatory mediators are said to exert pleiotropic effects on cancer development. On the one hand, inflammation favors carcinogenesis, malignant transformation, tumor growth, invasion and metastatic spread, but also inflammation is discussed as stimulating immune effector mechanisms that can limit tumor growth. The relationship between cancer and inflammation depends on signaling pathways

that lead to the activation of transcription factors and the accumulation of tumorigenic factors in the tumor and microenvironment. In our opinion, the activity of inflammation in periodontitis, which is reflected in the clinical parameter BOP, is more important than indicators of the severity of periodontitis for the development of a malignant lesion. Our results support the hypothesis of the importance of chronic inflammation in the oral cavity for the initiation of carcinogenesis.

Based on robust observational studies conducted since 1970, smoking and alcohol consumption have been identified as major risk factors for OSCC, with a well-defined dose-dependent effect [3, 10]. We may assume that oral carcinogenesis is a multistep process modulated by various endogenous and environmental factors. It is believed that smoking and regular alcohol consumption play a major role, leading to a wide range of events – genetic (irreversible changes in the DNA sequence) and epigenetic (changes in gene expression not encoded in the DNA sequence) that promote genomic instability and tumor development and progression.

CONCLUSION:

The results presented show an existing relationship between periodontitis and OSCC. The significantly higher value of bleeding on probing in patients with OSCC and periodontitis compared to those with periodontitis is indicative of the influence of inflammation in periodontal tissues for the development of a malignant process. The periodontal inflammation reflected in the BOP indicator is a process that can be reversed by periodontal therapy. The application of supra- and subgingival biofilm control procedures could be an effective approach not only to stabilize the periodontal condition and preserve teeth but also to reduce the risk of carcinogenesis.

Abbreviations:

OSCC – oral squamous cell carcinoma
OPMD – oral potentially malignant disorders
HPV – human papilloma virus
UV – ultra violet
BOP – bleeding on probing
PD – pocket depth
PDmax – pocket depth max
CAL – clinical attachment loss
CALmax – clinical attachment loss max

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