Diabetes and Oral Tumors in Hungary

Epidemiological correlations

MÁRTA UPÁL, DD1
ORSOLYA MATOS, DD1
GYÓRGY BÍROK, MD2

ANIKÓ SOMOGYI, PHD3
GYÓRGY SZABÓ, PHD3
ZSUZSANNA SUBA, PHD1

OBJECTIVE — Numerous publications have already demonstrated that diabetes is a risk factor for the development of periodontal diseases and various inflammatory lesions in the oral mucosa. A possible correlation between diabetes and oral premalignancies and tumors was examined in this study, as no literature data are available concerning this problem.

RESEARCH DESIGN AND METHODS — Stomato-oncological screening was carried out on 200 diabetic patients in the medical departments, the control group included 280 adult dentistry outpatients. The lesions found were classified into three groups: inflammatory lesions, benign tumors, and precancerous lesions. A retrospective diabetes screening of 610 inpatients with histologically confirmed oral malignancies was also performed. The control group comprised 574 complaint- and tumor-free adults. Fasting blood glucose levels were determined in both groups, and the tumor location was registered in the cancer patients.

RESULTS — Benign tumors were found in 14.5% and precancerous lesions in 8% of diabetic patients. In the control group these values were significantly lower, at 6.4 and 3.2%, respectively (P > 0.01). Earlier Hungarian screening studies indicated similar frequency of these lesions in the general population. The proportion of oral cavity lesions was higher among diabetic patients compared with that of the control patients. In the oral cancer patient group, diabetes was present in 14.6% and an elevated blood glucose level in 9.7%. These values are significantly higher than those for the tumor-free control group (P < 0.01). The gingival and labial tumor location was significantly more frequent among diabetic cancer patients than in the nondiabetic group (P < 0.01). The combination of diabetes and smoking means a higher risk for oral precancerous lesions and malignancies.

CONCLUSIONS — Diabetes may be a risk factor for oral premalignancies and tumors.

The inflammation-mediated carcinogenesis is a well-known empirical fact, but the exact pathway of this transition has not been perfectly clarified until now (6–9). Is there any correlation between diabetes and tumor genesis of the oral cavity? Surprisingly, there are no literature data concerning this problem. Accordingly, in the present study, we have attempted to look for such epidemiological associations.

Our first investigation involved the stomato-oncological screening of 200 diabetic patients. This was followed by a retrospective study of the incidence of diabetes and the tumor location in 610 patients with oral cancer.
were recorded on state of the teeth and
periodontium, mucosal lesions, precancerous, and tissue accumulations consid-
ered clinically to be benign or malignant. The examiners were not aware of the pa-
tients’ diabetic state. Whenever neces-
sary, the dates and locations of control or
treatment sessions were agreed on.

**Diabetes screening of oral cancer patients**

We studied 610 inpatients (435 men, 175 women) at the Department of Oral and Maxillofacial Surgery, Semmelweis University, with histologically confirmed ma-
lignant tumors in the oral cavity, between 1 January 1998 and 30 June 2002.

Histologically, 606 of them proved to be squamous cell carcinomas and 4 were adenocarcinomas. Their mean age was 56 years (range 36–85). The control group consisted of 574 tumor- and complaint-
free adults (351 men, 223 women) who volunteered to participate in stomato-
oncological screening. Their mean age was 51 years (range 32–78).

Fasting blood glucose levels were de-
termined repeatedly within 4 days. The level was regarded as elevated only if it was repeatedly elevated; if the repeated measurements included at least one neg-
ative result, the case was not considered pathological. All determinations were made using automatic analyzers (Hitachi 717/912; Roche Diagnostics Boehringer Mannheim, Mannheim, Germany). Based on the findings, the patients were classi-
ced into three groups: 1) patients with a normal fasting blood glucose level (<6.1
mmol/l), 2) patients with an elevated fast-
ing blood glucose level (6.1–6.9 mmol/l, impaired fasting glucose), and 3) patients with diabetes (>6.9 mmol/l).

The frequencies of malignant tumors at various locations in the oral cavity in the different groups were studied. The \( \chi^2 \)
test was used for the statistical analysis, and a probability level of 5% was taken as the limit of statistical significance.

**RESULTS**

**Stomato-oncological screening of diabetes patients**

The results are presented in Table 1. The lesions found were classified in three
groups: 1) inflammatory lesions, such as cheilitis and glossitis, 2) benign tissue accumulations, and 3) precancerous le-
sions, such as leukoplakia and erythro-
plakia. Malignant lesions were not found among these 200 diabetes patients nor in
the control group.

Some form of lesions of the oral cavity
was found in 51.5% of the diabetes pa-
tients. In both types of diabetes, inflam-
ations were the most frequent, followed
by benign tumors, and then by precancer-
ous states. In the control group, the fre-
cency of all lesions was significantly lower (\( P < 0.01 \)).

The proportions of inflammatory le-
sions (31.3 vs. 25.6%), benign lesions
(16.9 vs. 10.9%), and precancerous le-
sions (11 vs. 3.6%) were higher among patients with type 2 diabetes than among those with type 1 diabetes (Table 1).

The mean value of the HbA1c was
10.1% in the type 1 diabetes group and
7.2% in the type 2 diabetes group. It was
higher (7.7%) in the group of patients
with precancerous lesions. As it concerns
the state of the teeth, in the type 1 diabetes group, 12.7% of the patients were eden-
tulous or had subtotal tooth loss. A corre-
sponding serious state of the teeth was
found in 34.5% of the type 2 diabetes
group, in 16.2% of the control group, and
in 50% of the group with precancerous
lesions.

The most serious periodontal lesions
were found in the type 2 diabetes group;
gingivitis was found in 38% of the pa-
tients and periodontitis in 53%. In the
type 1 diabetes group, the frequency of
the gingivitis was 36% and that of par-
onodontitis 49%. In the control group, these
values were 29 and 45%, respectively.

Fifteen percent of the examined dia-
abetes patients were active smokers: 23% had given up smoking; the corresponding data were 12 vs. 16.9% and 21 vs. 24.5%, respectively, among those with type 1 and
type 2 diabetes. The 11% incidence of
leukoplakia in the group with type 2 dia-
betes was noteworthy. The proportions
of active smokers and of those who had
given up smoking in this group were 38
and 32%, respectively, i.e., a total of 70% who still were or had been smokers. The smoking diabetes patients were found to
include 16.6% with precancerous lesions
and 13.3% with benign lesions.

**Diabetes screening of oral cancer patients**

Blood glucose levels were elevated (6.1–
6.9 mmol/l) in 59 (9.7%) of the 610 pa-
tients with oral malignancies, and dia-
betes was present in 89 patients
(14.6%). Seventy-two of the diabetes pa-
tients were known cases, whereas 17
(2.8%) were newly diagnosed. Of the 72
known diabetes cases, 20 were being
treated with insulin, 52 with various oral
drugs, and 2 were on diets. Eighty-seven
(97%) of the 89 diabetes patients had type
2 diabetes.

The mean age in the diabetic group
was 60 years (range 42–91). The control
group was found to contain 32 (5.6%)
individuals with type 2 diabetes, 6 (1%)
of whom were freshly diagnosed cases.

Of the patients with malignant tu-
mors in the oral cavity, 14.6% had dia-
betes, whereas 9.7% displayed an elevated
fasting blood glucose level, i.e., overall,
24.3% of the patients had abnormal glu-
cose metabolism. There were significantly
more diabetes and elevated fasting blood
glucose cases in the tumor group than in
the control group: 5.6 and 5.5%, respectively ($P < 0.01$). The distributions of the malignant tumors in the oral cavity according to location for all of the patients and for the diabetes group are shown in Table 2. The most frequent malignant tumors among nondiabetic patients were sublingual carcinomas (146 patients, 28%), followed by lingual tumors (100 patients, 19%). By contrast, the most frequent oral cancers among the diabetic patients were gingival tumors (26 patients, 28%), followed by lingual tumors (100 patients, 24%). There were significantly more gingival and lip cancers in the diabetic group than in the nondiabetic group ($P < 0.01$).

In this study, 68% of all patients with malignant tumors and 30% of the tumorous diabetes patients were active smokers. The proportion of smokers in the control group was 27%.

**CONCLUSIONS** — According to the literature data, chronic inflammatory processes in the gastrointestinal tract (ulcerative colitis, Crohn disease) have an important role in carcinogenesis (8–10). Considering the well-known oral manifestations of diabetes (11–16), both the inflammatory processes (gingivitis, periodontitis) and the atrophic lesions (chronic cheilitis and glossitis) are possible precursors of malignant epithelial transformation. However, the epidemiological relationship between these two important diseases has not been studied until now. Recently, there are noteworthy epidemiological studies concerning the association between diabetes and transitional cell carcinoma of the bladder (17–20).

The first step was a stomato-oncological screening study to clarify the incidence of benign tumors and precancerous lesions in diabetic patients. We are aware of more stomato-oncological studies in Hungary between 1962 and 2000 (21,22). The present examinations revealed an incidence of benign tumors that was much higher than reported by other authors. Bánoczy et al. (21) found a frequency of 3.7% for the most common benign oral lesions. This was substantially lower than the 14.5% among our diabetes patients (10.9% for those of type 1 diabetes, and 16.9% for type 2 diabetes patients).

Albrecht et al. (16) found leukoplakia in 6.2% of their diabetes patients, whereas in the present study, an incidence of 6% for leukoplakia in diabetic patients was observed. Of the 16 precancerous lesions that were screened out, 4 proved to be erythroplakia, i.e., 2% of the 200 diabetes patients. This is markedly higher than the literature value of 0.1% (23).

The incidence of both precancerous lesions (leukoplakia and erythroplakia) was 8% in our diabetic patients: 3.6% in type 1 diabetes and 11% in type 2 diabetes. This latter value is essentially higher than the data of other Hungarian authors, who screened the general population for premalignant lesions (21). The state of the teeth was more serious in the group of patients with precancerous lesions. Although their mean age was higher than those of the other groups in the study, their serious loss of teeth can also be explained by their socioeconomic situation. The periodontal state of the patients in the type 1 diabetes group was not markedly worse than that of the control group. This can be explained first of all by the lower mean age of patients and by the fact that they have been treated and controlled for a long time. In the type 2 diabetes group, the serious periodontal state can be the result of the long-lasting uncontrolled or inadequately treated metabolic disorder.

The highest mean value of the HbA$_1c$ was found in the type 1 diabetes group. This finding suggests that hyperglycemia is not primarily responsible for the development of oral tumors and precancerous lesions. However, the insulin resistance in the type 2 diabetes patients, among other factors, may have an important role in the intraoral tissue proliferations. The tumor necrosis factor-$\alpha$ cytokine can give a plausible common pathway. It is a potential mediator of the insulin resistance and at the same time has a crucial role in the proliferation of certain tumors and metastatic spread (8,24).

The present study confirmed the well-known fact that smoking is a deciding risk factor for precancerous oral lesions (16,22,23,25–27). Seventy percent of our diabetes patients with leukoplakia were or had been smokers. The incidence of 16.6% for premalignant lesions (leukoplakia and erythroplakia) in this group of patients was extraordinarily high as compared with the data of Albrecht et al. (16). They reported an incidence of 11.5% for leukoplakia among smoking diabetes patients. It may be stated that smoking diabetes patients are a high-risk endangered group from the aspect of oral premalignancies.

The other aspect of this study was the diabetes screening of 610 inpatients with histologically confirmed oral malignancies. A majority of them had oral squamous cell carcinoma. There were significantly more patients with an abnormal glucose metabolism (24.3%) in the tumor group than in the control group (11.1%), and this difference proved to be significant ($P < 0.01$). Among our 89 tumorous, manifest diabetes patients, 87 (97%) had type 2 diabetes. Smoking and alcohol consumption are additional well-known risk factors for oral malignancies (26,27), so smokers and alcoholics among diabetic patients construe an extremely high-risk group.

The incidence of oral premalignancies and malignant tumors is also higher among socially disadvantaged groups (22); one of the etiological factors may be the undiagnosed and untreated type 2 diabetes. In the present study, the incidence of undiagnosed diabetes in oral cancer pa-

---

**Table 2** — Occurrence of oral cavity cancers among diabetic and nondiabetic patients

<table>
<thead>
<tr>
<th>Location of oral cavity cancers</th>
<th>Labial</th>
<th>Lingual</th>
<th>Sublingual</th>
<th>Gingival</th>
<th>Buccal</th>
<th>Other</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nondiabetic patients</td>
<td>73 (14%)</td>
<td>100 (19%)</td>
<td>146 (28%)</td>
<td>83 (16%)</td>
<td>21 (4%)</td>
<td>98 (19%)</td>
<td>521 (100%)</td>
</tr>
<tr>
<td>Diabetic patients</td>
<td>21 (24%)</td>
<td>16 (18%)</td>
<td>13 (15%)</td>
<td>26 (29%)</td>
<td>3 (3%)</td>
<td>10 (11%)</td>
<td>89 (100%)</td>
</tr>
<tr>
<td>Total</td>
<td>94</td>
<td>116</td>
<td>159</td>
<td>109</td>
<td>24</td>
<td>108</td>
<td>610</td>
</tr>
</tbody>
</table>

Data are $n$ (%).
tients was 2.8%, which was three times higher than in the control group. In addition, the precancerous and tumorous oral lesions are surprisingly more frequent in type 2 than type 1 diabetes. Possible etiological factors may be partly the above-mentioned insulin resistance or partly the fact that type 2 diabetes cases are generally diagnosed and treated after a longer delay, as the complaint-free latency period can take several years (28).

As concerns the location of oral malignancies, in the nondiabetic group, the lingual and sublingual tumors were dominant. In the diabetes group, the most frequent locations of cancer were the gingiva and the lower lip, which are also preferentially affected by inflammatory lesions in diabetic patients (29,30).

There are numerous literature data on the inflammatory lesions of the periodontal tissues and the oral mucosa in diabetes patients (2,3,5,12,31). These oral alterations are more serious in untreated or inadequately treated diabetic patients (3,5,29). The details of the metabolic alterations and the tissue alterations in diabetes are not completely revealed, although the literature data are numerous (12,29,31,32).

In diabetes, the oxidation equilibrium breaks down. The elevated glucose concentration, the excessive formation of free radicals, and the protein glycation depress the activities of the antioxidant scavengers and enzymes. These noxious processes can cause serious damages in the biological structures even at a molecular level (32,33). The role of free radicals and the oxidative stress in the carcinogenesis is a well-known fact (8,10). The advantageous therapeutic effects of the antioxidants can be used successfully in the tumor treatment, even in cases of oral malignancies (25). Many authors have demonstrated a defect of the first step in the defense mechanism, a decreased chemotactic migration of the polymorphonuclear leukocytes in poorly treated diabetes cases. The T-cell function and the cellular immune response are also impaired (12).

The tissue hypoxia caused by the microangiopathic lesions of the gingiva in diabetes were first described by Ray (11). The hyperglycemia can provoke agglutination of the formal blood elements, which leads to microembolization. These changes are primarily observed in poorly or inadequately treated patients (11,29). The exact pathomechanism of the diabetic tissue disorder or that of the malignant transformation is not clarified, but the microvascular changes, the secondary hypoxia, the impaired immunological defense mechanism, and the breakdown of the oxidation equilibrium can play a complex role in the development of oral lesions. The crucial pathway of inflammatory-mediated carcinogenesis in diabetes remains to be revealed.

The present study suggests a novel hypothesis for an etiological association between diabetes and precancerous and tumorous lesions of the oral cavity. Confirmation of these findings requires further studies.

References