

Prevalence of Diabetes and Impaired Fasting Glycemia in Patients With Oral Cancer: A Retrospective Study in Hungary

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Abstract. *Background/Aim:* Diabetes mellitus (DM) is one of the most common chronic metabolic disorders. Our research aimed to demonstrate the relationship between DM and oral cancer. *Patients and Methods:* We pursued a retrospective research study in Hungary between January 2019 and December 2020. We investigated 597 inpatient records and compared them to the results of our previous studies (1998-2002 and 2012-2015). *Results:* The frequency of patients with DM in the oral cancer group is 2.45 times higher today than 20 years ago. The prevalence rate of DM and oral malignancies increased from 14.6% to 35.8%. In the oral cancer group, 54.4% of the patients had elevated blood glucose levels and of these, 61.1% of them had type 2 diabetes, 34.2% had impaired fasting glycemia, and only 4.7% had type 1 diabetes. We observed that 45.3% of them were smokers. Of those whose blood sugar levels were under 6.1 mmol/l, the mean body mass index was 25.33 [standard deviation (SD)= ± 4.5 ; range=15.57-39.84], while among patients with DM, it was 26.92 (SD= ± 5.8 ; range=18.36-44.08). *Conclusion:* It may be necessary to continuously monitor the patient's blood sugar level to maintain euglycemic levels when managing patients with malignant oral lesions.

Diabetes mellitus (DM) is one of the most common chronic metabolic disorders characterized by elevated blood glucose levels. The pathophysiology of this disease is secondary to insulin secretion deficiency, dysfunction, or both (1). It has three main types: type 1 diabetes (T1D), type 2 diabetes (T2D), and gestational diabetes (GDM) (2). Unfortunately, there is an increasing trend in the number of patients living with diabetes (3). Most patients have T2D, which is preventable with a healthy lifestyle (4). In 2017, 451 million people were living with DM worldwide. According to the International Diabetes Foundation Atlas data, researchers predict this number to climb to 693 million by 2045 (5). According to the Hungarian Diabetes Association, more than 700,000 people are living with DM in Hungary. The prevalence of patients with diabetes and impaired fasting glycemia (IFG) in Hungary is 7.5% and 4%, respectively (6). The prevalence rate of T2D is noted to increase with age. The prevalence rate is 19% in people aged 60-70 years whereas it is 20% in those aged >70 years (7).

DM can cause serious, potentially life-threatening complications such as kidney failure (8), cardiovascular diseases (9), microangiopathy (10), retinopathy (11), and neuropathy (12). Moreover, DM can severely damage oral tissues. It increases the risk of periodontal diseases and tooth loss (13, 14), especially in combination with uncontrolled glycemia. People living with diabetes often experience xerostomia (15) and burning mouth syndrome (16), which usually lead to tasting dysfunctions (17). After oral surgeries, delayed wound healing can cause complications, such as dry sockets (18). Geographic tongue (19), lichen planus (20), and oral candidiasis (21) are more common among people with DM (22). Oral malignancies may be more prevalent in patients with DM. We aimed to demonstrate the relationship between DM and oral malignancies in this study.

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Table I. Comparing the results of three different examination intervals.

	Oral cancer group			Control group		
	1998-2002	2012-2015	2019-2020	1998-2002	2012-2015	2019-2020
Number of participants	610	758	274	574	534	323
Men	71.3%	52.8%	54.7%	61.1%	59.6%	63.5%
Women	28.7%	47.2%	45.3%	38.9%	40.4%	36.5%
Mean age (years)	56	64	68	51	53	47
Frequency of diabetes	14.6%	25.9%	35.8%	5.6%	10.3%	8.0%
T1D	2.2%	2.0%	7.1%			
T2D	97.8%	98.0%	92.9%			
Frequency of IFG	9.7%	20.6%	18.6%	5.5%	10.5%	9.9%
Proportion of smokers	68.0%	57.7%	45.3%	27.0%	41.2%	35.9%

IFG: Impaired fasting glycemia.

Patients and Methods

Data collection. This is a retrospective research study conducted at the Semmelweis University, Department of Oral and Maxillofacial Surgery, Budapest, Hungary between January 1, 2019 and December 31, 2020. We included 597 inpatient medical records. We recorded the following information: age, sex, height, weight, smoking habits, presence of diabetes or IFG, and cause of the hospital admission. For patients diagnosed with oral malignancy, we registered the location of the tumor and its histological type. Body mass index was calculated as patient's weight in kg/(patient's height in m)². Exclusion criteria included patients under 18 years of age and those with a history of drug abuse.

We classified patients into the diabetes group if they were previously diagnosed with DM. IFG was considered for patients with fasting blood glucose levels between 6.1 mmol/l and 6.9 mmol/l (23). We divided the participants into two groups, namely those diagnosed with oral malignancy as the experimental/oral cancer group and those without, the control group.

All data were stored using Microsoft Excel. Our research group conducted similar studies twice in the past 20 years [1998-2002 (24) and 2012-2015 (25)]. We compared our collected data from this study to the results of these previous studies (Table I).

Ethical approval. The study was conducted in accordance with the Declaration of Helsinki Ethical Principles and Good Clinical Practices and was approved at each site by the Ethical Committee of the Semmelweis University (Budapest, Hungary) (Ethical Approval Number: SE-RKEB 204/2018).

Statistical analysis. Data analysis was performed using Prism version 8.4.2 (464) software (Graphpad Software, San Diego, CA, USA) and data were reported as means±standard deviations (SDs) and range or absolute numbers with percentages. We used Pearson's Chi-squared test for statistical analysis. Differences below the 5% limit ($p<0.05$) were considered significant.

Results

Of the 597 patients included in the study, the experimental group included 274 patients (45.9%), comprising 150 men and 124 women. All patients were diagnosed with oral

malignancies that were confirmed histologically. The mean age of the oral cancer group was 68 years (± 12.9 ; range=33-96 years). Of the oral cancer group, 45.3% (124/274) were smokers. Approximately half of the patients with cancer, 54.4% (149/274), had elevated blood glucose levels. Of these patients, 61.1% (91/149) were diagnosed with T2D, 34.2% (51/149) were classified into the IFG group, and only 4.7% (7/149) had T1D. The mean BMI was 25.33 (± 4.5 ; range=15.57-39.84) for those whose blood sugar levels were under 6.1 mmol/l and 26.92 (± 5.8 ; range=18.36-44.08) for those with DM. Based on the histological examination, the most common neoplasm was squamous cell carcinoma (85%, 233/274). The remainder consisted of basal cell carcinomas (6%, 17/274), melanomas (1%, 3/274), adenoid cystic carcinoma (1%, 4/274), adenocarcinomas (1%, 4/274), and other rarer types of malignancies. Most malignant tumors were located on the lips (28.8%, 79/274), tongue (19.0%, 52/274), sublingual region (18.6%, 51/274), or gingiva (11.3%, 31/274). The prevalence of tumors in different locations was almost equal in patients with and without DM. The control group had 323 patients, comprising 206 men and 118 women. The mean age of the control group was 47 years (± 17.3 ; range=18-91 years). Patients of this group were hospitalized due to facial trauma causing fractures of the mandible or midface (45.5%, 147/323), orthognathic surgery (15.8%, 5/323), surgical removal of benign tumors (11.8%, 38/323), cysts of the jaws (22.9%, 74/323), or treatment of other benign lesions (4%, 13/323). We noted that the control group had 18.0% patients (58/323) diagnosed with glucose metabolic disorders, of whom 9.9% (32/323) were with IFG and 8.0% (26/323) with diabetes. The prevalence of DM and IFG among patients with cancer were 35.8% (98/323) and 18.6% (51/323), respectively. Based on the statistical analysis, we concluded a significant difference between the two groups (DM groups $p<0.00001$ vs. IFG groups $p=0.002185$). More than one-third of the control group were smokers (35.9%,

116/323), which had a statistically significant difference with the oral cancer group (45.3%, 124/274; $p=0.020346$).

Discussion

In this study, we aimed to demonstrate the relationship between DM and oral malignancies. This paper discussed the relationship between DM, smoking, and malignant oral lesions in terms of sex and age. We have shown that trends differ between the 1998-2002 and 2019-2020 periods in terms of average age, sex, DM incidence, and percentage of smokers. During the past decades, the incidence of oral cancer in patients with DM has increased by 2.5 times.

DM is one of the most significant public health diseases. For the past decades, it has been showing an alarming increase in incidence rates. Similar trends can be observed in terms of malignant oral lesions, wherein Hungary ranks among the highest in Europe in terms of morbidity and mortality rates (26).

Elevated glucose level accelerates the synthesis of tumor cell DNA and causes failure in oxidative balance mechanisms. It leads to the release of a multitude of growth factors and cytokines, which molecules facilitate the growth and spread of malignant cells. New advances in cancer therapy, like additional corticosteroid therapy, inhibit the translocation of GLUT-4 glucose transporter or mTOR inhibitors (PI3-K inhibitors), positively affecting the oncologic status. The specific mechanism remains unclear but understanding the relationship between neoadjuvant therapies and secondary diabetes could determine the optimum care for patients (27).

On comparing the results of this study with our previous data, we noted that the frequency of people with DM in the oral cancer group is 2.45 times higher today than 20 years ago. The incidence of confirmed DM had a statistically significant increase from 14.6% to 25.9% until 2015 and to 35.8% until 2020 ($p=0.000657$). Although the number of people with DM showed a rapid increase, the current proportion of people with IFG is in the same range as in 2015. For the oral cancer group, the demographics in terms of age and sex differed from that of our previous studies. The mean age of people in the current oral cancer group was 68 years compared to the mean of 56 years previously. Similarly, the ratio of women increased from 28.7% in 1998 to 45.3% in 2020. The frequency of smoking shows a decreasing tendency both in the oral cancer and control groups. The proportion of smokers in the oral cancer group almost halved from 68% in our first study to 35.9% in this study. In the control group, there was an increase in the number of smokers between 1998 and 2015 from 28% to 41.2% that later declined to 35.9%. This may be because of the positive impacts of the strict laws and regulations of tobacco product selling in Hungary.

The incidence of DM among people with oral cancer has increased from 14.6% to 35.8% during the last 20 years. The increase in mean age may partly explain this trend because

most people in our study were diagnosed with T2D, which is more common among the elderly. The increase in mean age can also result from the different ratio of men to women, which was 28.7%-71.3% in the 1998-2002 study and 45.3%-54.7% in the current study. Malignant lesions in women are primarily diagnosed 15-20 years after menopause.

Compared to the studies conducted 20 years ago, the incidence of diabetes, particularly T2D, has doubled among those with cancer. Because metabolic conditions associated with DM also affect tumor metabolism, treatment may result in tumor recurrence. Metformin, the primary drug of choice for the treatment of T2D achieved good results. Even the non-diabetic patients responded better to neoadjuvant and radiotherapy treatments (28), and patients with diabetes had a better tumor-specific two-year survival rate (29).

People with diabetes are considered a high-risk group in terms of dental diseases. Dental screening and care should be one of the pillars of comprehensive diabetes care, which is an opportunity we would like to create in the future. For people living with T2D, we recommend at least an annual dental check-up, which includes a stomato-oncological screening examination. Since 2015, our team has worked on the goal to better understand problems that arise during the dental care of patients with diabetes using our data and to help improve the quality of the patient's lives with these tests and experimental results (30). We were in constant collaboration with the Hungarian Diabetes Association, the International Diabetes Federation, and the dental department of the Hungarian Medical Association during these study periods. At Semmelweis University, Budapest, we provide free dental screening to patients with diabetes. This service is currently unique in the world. The purpose of the specialist clinic is that the annual dental check-up of patients diagnosed with diabetes should be integrated into clinical practice. We believe that prevention is the key to success.

In conclusion, we showed a significant increase in patients with diabetes and oral cancer. It may be necessary to continuously monitor the patient's blood sugar level and maintain it at euglycemic levels when managing patients with malignant oral lesions. Future research should evaluate whether dental screening programs are effective in detecting premalignant oral lesions in patients with diabetes.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

AV, DV: Conceptualization, Methodology, Software. DB, MU, PH, ZN: Data curation, Writing- Original draft preparation, Visualization, Investigation. SKS, ZB, GK: Supervision. MU, MP: Software, Validation. DV, MU: Writing- Reviewing and Editing.

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