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Point-of-care HbA1c Measurements in Oral Cancer and Control Patients in Hungary

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Abstract. *Background/Aim: This study aimed to investigate the link between preoperative glycated hemoglobin (HbA1c) levels and oral cancer patients and diabetes mellitus (DM). We aimed to highlight the importance of point-of-care HbA1c measurements in oral cancer patients. Patients and Methods: A total of 214 patients were admitted to the Department of Inpatient Care at Semmelweis University's Department of Oromaxillofacial Surgery and Stomatology between 1 September 2020 and 21 May 2021; individuals, who had undergone maxillofacial surgery under general anesthesia, were included in the study. Results: There was a significant difference between the oral cancer group and the control group in terms of smoking (p=0.009) and alcohol intake (p=0.003). There was no statistically significant difference regarding sex (p=0.132) and DM (p=0.147) between the two groups. The tumor group had an 8.52% greater prevalence of DM, which was not significant. In the oral cancer group, twenty individuals (17.69%) had a higher HbA1c level than the upper level of the optimal metabolic value (6.9%). Nine participants (8.91%) in the control group had an HbA1c value greater than 6.9%, which means that their metabolic level was poor. The oral cancer group did not have higher blood glucose levels than those of the control group. Conclusion: No direct connection between high blood glucose levels and oral cancer was found. However, point-of-care HbA1c measurement can be a diagnostic tool to detect DM in the dental office.*

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Diabetes mellitus (DM) is a metabolic disorder that is primarily characterized by hyperglycemia. DM is caused by inadequate insulin production, insulin action, or both. There are various forms of DM, the most common being Type 1 (T1DM) and Type 2 (T2DM); nevertheless, there are subtypes such as Gestational DM. According to the International Diabetes Federation (IDF), DM affects around 420 million people globally and 700,000 people in Hungary (1). T1DM develops rapidly due to a variety of environmental and internal variables – the primary mechanism of which is unknown – and must be treated with intensive insulin therapy. T2DM typically develops over years or decades, and a strong association exists between T2DM and obesity, poor diet, and sedentary lifestyle. T2DM therapy is highly dependent on

the development of the disease. Patients with T2DM have frequently prescribed biguanides (most commonly metformin), DPP-4 inhibitors (sitagliptin), and SGLT-2 inhibitors (dapagliflozin) (2). All of these medications are intended to lower blood sugar levels by enhancing glucose uptake by cells, increasing insulin secretion, or, in the latter case, limiting glucose absorption in the intestine. Without the appropriate lifestyle changes and medicine, chronic illness can proceed rapidly when cells have an insulin output that is so low that even those who live with T2DM require insulin supplementation. T2DM is often associated with obesity and occurs as a consequence of a combined impairment in insulin secretion and insulin action. β-cell failure of T2DM has a metabolic component, which means that the lack of insulin production causes a need for external insulin injections, such as in T1DM (3). DM is diagnosed by monitoring fasting or random plasma glucose levels, the Oral Glucose Tolerance Test (OGGT), and/or by monitoring glycated hemoglobin (HbA1c) values (4, 5). DM patients have a ≥7.0 mmol/l fasting sugar level, an OGTT sugar level ≥11.1 mmol/l, or an Hba1c level ≥6.5% (6). Screening patient fasting plasma glucose levels is the first step in diagnosing DM. Based on the recommendations of the American Diabetes Association (ADA), an FPG under 5.6 mmol/l is considered to be a standard-base value, with 5.6-6.9 mmol/l being the desired impaired glucose fasting (IFG) level. The HbA1c levels indicate the proportion of glycated to non-glycated hemoglobin in the blood. These data provide medical practitioners with information about a patient's average glucose levels over the last 3 months. It offers the advantage of obtaining information for an extended period of time and is less affected by transient factors (7). There are two methods for determining HbA1c levels: laboratory testing and point-of-care (POC) HbA1c testing. PoC is defined as the testing method that can be evaluated in the dental office from a finger blood sample, making the procedure easy for both the operator and the patient (6). The fast availability of HbA1c levels (3-6 min) enables the data to be discussed face-to-face, improving patient-doctor communication and satisfaction, and improving glucose management (8). When combined with a comprehensive quality management system, HbA1c testing has been shown to enhance DM treatment (9). Regrettably, it is rarely used to diagnose the disease but rather to assess the efficacy of various treatments, diets, and lifestyle changes. An HbA1c level of less than 5.6% is considered normal, between 5.7% and 6.4% indicates prediabetes, and over 7% indicates DM.

Chronic hyperglycemia and DM can result in various serious complications, including angiopathy, neuropathy, nephropathy, and retinopathy, and are increasingly being linked to the development of malignant tumors, including those found in colon, kidney, liver, endometrial, breast, and pancreatic cancer (10). Several studies have found that people with DM had an increased risk of oral cancer (11). Metformin use in people with DM may explain a negative correlation between DM and some types of cancer (12).

Patients and Methods

This study aimed to investigate the link between oral cancer, DM, and preoperative glycated hemoglobin (HbA1c) levels. We aimed to highlight the importance of point-of-care HbA1c measurements in oral cancer patients. This case-control study was conducted between September 1, 2020, and May 21, 2021, at the Department of Oral and Maxillofacial Surgery, Semmelweis University, Budapest, Hungary. A total of 214 patients were admitted to the Department of Inpatient Care at the Department of Oromaxillofacial Surgery and Stomatology of Semmelweis University during this period. The study protocol was designed by the Semmelweis University Diabetes-Dental Research Group.

Participants were split into two groups: those diagnosed with an oral malignancy were assigned to the oral cancer group, while those not assigned to the oral cancer group were assigned to the control group. The control group included patients who had dentoalveolar surgeries in the clinic (benign tumor surgeries, orthognathic surgeries, or maxillofacial surgeries). We collected the following data: sexual orientation, smoking and drinking habits, DM diagnosis, and hospitalization reasons. We recorded the site of the tumor and its histological type in the individuals who had been diagnosed with oral malignancy. Patients who were under 18 years of age and those with a history of substance misuse were excluded.

Diagnostic measurements. Next, we determined the patients' fasting blood glucose and HbA1c levels. Measurements were conducted in the morning on an empty stomach. For the blood glucose testing we used DCONT Hunor (77 Elektronika, Budapest, Hungary). For the HbA1c testing we used SmartTester® (77 Elektronika). SmartTester is a quantitative rapid test reader recommended for professional *in vitro* diagnostic (IVD) use based on chromatographic immunoassay. Finger blood was used for the analysis. An HbA1c level of 6.9% (8.41 mmol/l) was chosen as a cut-off point. We visualized the research findings graphically and then conducted the statistical analysis.

Ethics. The study was conducted according to the Declaration of Helsinki Ethical Principles and Good Clinical Practices and was approved by the Ethical Committee of the Semmelweis University (Budapest, Hungary) (Ethical Approval Number: SE-RKEB 204/2018). Informed consent was obtained from all subjects involved in the study.

Statistical analysis. Data analysis was performed using Prism version 8.4.2. (464) software (Graphpad Software, San Diego, CA, USA). We used Pearson's Chi-squared test for statistical analysis. Differences below the 5% limit ($p<0.05$) were considered significant. All data were stored using Microsoft Excel (Microsoft Inc., Redmond, WA, USA).

Results

A total of 214 people were enrolled in this study. The oral cancer group consisted of 113 individuals ($n=113$), whereas the control group consisted of 101 patients ($n=101$). The following features describe the cancer group: There were 62 men (54.87%) and 51 women (45.13%). A total of 39 were smokers (34.1% of the population), and 74 were nonsmokers (65.49%). There were 30 patients who consumed alcohol

Table I. *Select characteristics of the study sample.*

		Oral cancer group n=113	Control group n=101	*p*-Value
		n	n	
Sex	Male	62 (54.87%)	45 (44.55%)	0.132
	Female	51 (45.13%)	56 (55.45%)	
Smoking status	Smokers	39 (34.51%)	15 (14.85%)	0.009
	Non smokers	74 (65.49%)	86 (85.15%)	
Alcohol status	Alcoholic	30 (26.55%)	11 (10.89%)	0.003
	Non-alcoholic	83 (73.45%)	90 (89.11%)	
Presence of DM	DM	32 (28.32%)	20 (19.80%)	0.147
	Non-DM	81 (71.68%)	81 (80.20%)	
Localization of cancer.	Hard palate	8 (7.08%)		
	Pharynx	11 (9.73%)		
	Gingiva	30 (26.55%)		
	Labium sup.	4 (3.54%)		
	Labium inf.	14 (12.39%)		
	Lingual	26 (23.01%)		
	Soft palate	4 (3.54%)		
	Sublingual	16 (14.16%)		

DM: Diabetes mellitus.

regularly (26.55%), whereas 83 people abstained from alcohol (73.45%). A total of 32 patients (28.32%) had been diagnosed with DM, while 81 people did not disclose a DM diagnosis during anamnesis (71.68%). The control group consisted of 45 men (44.55%) and 56 women (55.45%). A total of 15 of them (14.85%) were smokers, whereas 86 were nonsmokers (85.15%). There were 11 patients (10.89%) who consumed alcohol regularly, whereas 90 patients abstained from alcohol (89.11%). A total of 20 patients had been diagnosed with DM (19.80%), while 81 patients had no recollection of being diagnosed with the ailment (80.20%). There was a significant difference between the two groups in terms of smoking (p=0.009) and alcohol intake (p=0.003). We found no significant differences in terms of sex (p=0.132) or DM (p=0.147) between the two groups. Male patients with oral cancer had a prevalence that was 9.74% higher than the female patients in the oral cancer group. The proportion of women was 10% higher than the proportion of men in the control group. Comparison of DM prevalence between the two groups, indicated that the tumor group had an 8.52% greater prevalence of DM. In light of the intraoral site of the tumors, we obtained the following outcomes: gingiva 30 (26.55%), lingual 26 (23.01%), sublingual 16 (14.16%), labium inf. 14 (12.39%), pharynx 11 (9.73%), hard palate 8 (7.08%), soft palate 4 (3.54%), labium sup. 4 (3.54%), pharynx 11 (9.73%), pharynx 11 (9.73%), hard palate 8 (7.08%), and soft palate 4 (3.54%) (Table I). Table II presents the average HbA1c-levels in different patient groups. The results showed that the blood glucose levels of the control group were higher than those of the tumour group.

Among the malignant tumors (n=113), 104 were planocellular carcinoma (92.0%), five were adenoid cystic carcinoma (4.4%), one mucoepidermoid carcinoma (0.9%), one verrucous carcinoma (0.9%), one schwannoma with malignant transformation (0.9%), and one prostate cancer metastasis (0.9%) (Table III).

Twenty individuals from the control group (17.69%) had HbA1c levels higher than the oral cancer group's average level of 6.9%. Nine participants (8.91%) in the control group had a value greater than the limit. It is worth noting that most of the smokers and alcoholics in the tumor group did not have DM (Table IV).

Discussion

Numerous articles- have been published on how oral cancer, smoking, DM, and alcohol intake influence each other (13-19). Our research team was among the first to identify a strong correlation between DM and malignant oral cancers (20-23) and MRONJ (24) both in Hungary and Austria (25) This issue is also addressed in the current study. This study explored the association between DM, smoking, alcohol intake, and malignant oral lesions in terms of sex and age. In this study, DM was 8.52% more prevalent in the tumor group than in the control group. It should be highlighted that we only included DM in the study if a diabetologist had previously diagnosed the patient with the condition. DM may also be suspected to occur in other patients based on HbA1c level measurements. These data also demonstrate the critical value of HbA1c level assessment.

Table II. *The average HbA1C-levels in different patient groups.*

	Oral cancer group		Control group	
	HbA1C-level (%)	Fasting blood glucose level (mmol/l)	HbA1C-level (%)	Fasting blood glucose level (mmol/l)
All patients	5.68	5.89	6.34	6
Men	5.56	5.68	6.2	6.04
Women	5.8	6.13	6.16	5.93
Patients with DM	6.42	7.1	7.57	7.31
Men with DM	6.58	7.71	7.98	7.56
Women with DM	6.37	6.78	7.28	7.12
Patients without DM	5.35	5.47	5.46	5.72
Men without DM	5.3	5.29	5.44	5.55
Women without DM	5.48	5.78	5.53	5.93

DM: Diabetes mellitus; HbA1C: glycated hemoglobin.

Table III. *Histological classification of the malignant tumors.*

	(n)	(%)
Planocellular carcinoma	104	92.0
Prostate cancer metastasis	1	0.9
Adenoid cystic carcinoma	5	4.4
Mucoepidermoid carcinoma	1	0.9
Verrucous carcinoma	1	0.9
Schwannoma with malignant transformation	1	0.9

Table IV. *Confidence intervals of oral cancer according to HbA1c level, smoking, and alcohol consumption.*

	Groups				*p*-Value
	Oral cancer group		Control group		
HbA1C>6.9%					
Non-DM	3	(2.7%)	2	(2.0%)	0.633
DM	17	(15.0%)	7	(6.9%)	
Smoke					
Non-DM	33	(29.2%)	10	(9.9%)	0.142
DM	6	(5.3%)	5	(4.95%)	
Alcohol					
Non-DM	24	(21.2%)	5	(4.95%)	0.031
DM	6	(5.3%)	6	(5.94%)	

DM: Diabetes mellitus; HbA1C: glycated hemoglobin.

Obesity and high glycemic levels were associated with an increased risk of all sites, breast, and liver cancer, and cancer-specific death in T2DM. Several factors promote the spread of malignant tumors in DM patients. In T2DM the permanent hyperglycemic condition generates the release of free radicals and oxidative stress. (26). Oral Magnesium supplementation could influence glycemic control in T2DM patients (27). An American study showed that non-obese patients with cancer had higher odds of cancer death. Rising HbA1c and increasing age were associated with increased cancer mortality (28). We now have moderate-certainty evidence that periodontal treatment using subgingival instrumentation significantly improves glycemic control in people with both periodontitis and DM compared to no treatment or usual care (29). The study findings support the Mediterranean dietary model as a suitable model for T2DM and the concept that the beneficial health effects of the Mediterranean diet lie primarily in the synergy among various nutrients and foods rather than on any individual component (30). There can be a substantial discordance between laboratory and eA1C (continuous glucose monitoring-estimated HbA1c) levels in a real-world setting. Clinicians need to be aware that HbA1c may not as accurately reflect mean glucose as previously appreciated. POC HbA1c measurement in the dental office should be a warning and a first-line indication of the metabolic status. The authors would like to highlight, that laboratory measurement of HbA1c by a diabetologist in an internal medicine department should be used for the diagnosis of metabolic disorders such as DM. The dentist has an important role in DM care, but further examination and proper diagnosis are not his/her responsibility (31). Oral squamous cell carcinoma patients with higher preoperative HbA1c levels had longer hospitalization and worse survival outcomes (32).

Taking the above into account, we expected to obtain a higher percentage of HbA1c levels in the tumor group compared to the control group. However, to our surprise, the control group had higher instantaneous blood glucose values. Accordingly, we need to reassess our current ideas about the relationship between oral cancers and diabetes mellitus. In our opinion, it is not necessarily the higher average blood

glucose level that increases the likelihood of developing tumors, but rather its fluctuating nature. Patients with DM may have more extreme values of blood glucose, either too high or too low. Such fluctuations in blood glucose levels can be tumorigenic. Proving this hypothesis, however, requires close patient control and decades of follow-up, conditions that were not present in this study.

It is questionable whether POC HbA1 is an important tool to detect metabolic disorders, or track the status of the therapy. Studies from 2010 and onwards show controversial data on the use of POC instruments for diagnosis: only a few devices meet the acceptable performance criteria and how the test will perform in the hands of non-professionals is questionable (33). The authors' opinion is that in dental office diagnosis of DM is not the responsibility of the dentist, however a very important prevention stage, as if abnormal values are being detected, further interdisciplinary approach is possible by DM care providers. In the last decade, the technological change in DM care is remarkable, as insulin pumps, CGM and blood glucose meters are very accurate, and closed-loop systems are playing a key role in the treatment of T1DM care. HbA1c diagnostic tools have also developed significantly, and the accuracy is comparable with the laboratory diagnostic tools. From a patient perspective, these tests are fast and more comfortable as the sample is from finger blood instead of the common venous blood sampling. A wide range of studies showed the accuracy of HbA1c instruments (34, 35). Another valuable point regarding the POC instruments is the access to medical devices. From a global point of view, expensive laboratory devices are not accessible everywhere and can be financial burdens for local hospitals. POC machines are cheaper, and the test strips are also affordable as they cost 3-10 euros per stick on average (36). This could be a perfect solution to widen the access to medical care and help to diagnose DM in an early stage and to eliminate the long-term side effects of DM. Norwegian community pharmacies perform internal quality control (IQA) and EQA on an HbA1c POC instrument, and the performance is comparable with that of GP offices. The compliance in the EQA surveys was modest, but the duration of the study and participation in the EQA program was probably too short to implement all the new procedures for all pharmacies (37). Ambulatory clinics are using POC HbA1c testing as an effective solution - for the medical and dental professionals - to give feedback about the metabolic status (38). Another USA-based study showed that POC and HPLC provide evidence for good concordance (39).

We describe an inexpensive, simple to implement and accurate method for obtaining HbA1c results in remote clinics, which have good patient acceptance and overcome the many challenges that have hampered dried blood sample (DBS) and volumetric absorptive microsampling (VAMS) blood collection. In addition to necessary face-to-face consultations, virtual consultations supported by remote HbA1c testing as described above will be a significant advance in diabetes care (40).

The investigation has several limitations, such as the comparison of the POC HbA1c data with a high-performance liquid chromatography (HPLC) dataset. For the future, the postsurgical complications can be further investigated taking into account the presurgical metabolic data, in conjunction with the international recommended thresholds.

Conclusion

In conclusion, our research addressed several critical etiological variables for malignant oral cancers. We consider it essential to have an annual dental check-up for people living with DM and maintain blood glucose levels of these patients in the normal range in order to prevent premalignant and malignant oral lesions. POC HbA1c measuring is a fast and reliable tool to have a quick estimation of the metabolic status of our patients before oral cancer surgeries. Interdisciplinary cooperation is necessary to provide the best oral treatment to patients who are at risk of metabolic disorders and/or oral cancer. This study used only the POC HbA1c device, as HbA1c control is not a regular examination before oral surgeries with or without oral cancer. This examination could support some future changes in the oral care of patients with DM, and oral tumor patients could have a more detailed examination before surgery.

The time-in-range (TIR) is also very important in patients with DM, and the extreme changes in the glucose spikes could have an effect on the tumor incidence. Therefore, a more detailed investigation of this very specific patient population (oral cancer group), probably with CGM settings, is required.

POC HbA1c represents a cost-effective, reproducible, and clinically significant tool for the management of DM in an outpatient setting, allowing the rapid recognition of high-risk patients and appropriate referral to secondary DM services (41-43).

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Conflicts of Interest

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

Authors' Contributions

Conceptualization, Adam Vegh, Daniel Vegh, Dorottya Bányai, Gabor Kammerhofer, Zita Biczo, Juan Pena Francisco Cardelles, Zehra Yonel, Arpad Joob-Fancsaly, Peter Hermann and Zsolt Nemeth; Investigation, Gabor Kammerhofer and Zita Biczo;

Methodology, Dorottya Bányai and Balazs Voros; Supervision, Arpad Joob-Fancsaly and Zsolt Nemeth; Writing – original draft, Adam Vegh, Daniel Vegh and Juan Pena Francisco Cardelles; Writing – review & editing, Marta Ujpal and Zehra Yonel.

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