ANTICANCER RESEARCH *42*: 1899-1903 (2022)
doi:10.21873/anticanres.15666

Diabetes Mellitus and Oral Cancer: A Retrospective Study from Austria

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Abstract. *Aim: This study aimed to analyse the possible linkage between diabetes mellitus (DM) and oral cancer among Austrians. Patients and Methods: We performed a retrospective DM and/or impaired fasting glucose (IFG) screening in 573 patients who underwent maxillofacial surgery under general anaesthesia between January 1, 2018 and December 31, 2019. Results: Of the total patients, 26.5% (n=152) had cancer diagnosis, whereas the remaining 73.5% (n=421) formed the control group. The prevalence of glucose metabolism disorder (GMD) was significantly (p<0.00001) more common among cancer patients (59.9% vs. 36.5%). Squamous cell carcinoma and sublingual tumours represented the most common tumour type (93.4%) and location (35.5%), respectively. Smoking was significantly (p=0.00093) more common within the cancer group. Conclusion: Our data suggest an association between GMD and oral cancer.*

Diabetes mellitus (DM) ranks among the most common chronic disorders and causes of death worldwide. According to the World Health Organization estimations, around 422 million people lived with DM in 2014. Although DM has always been associated with Western lifestyle (*e.g.* hypercaloric diet and physical inactivity), the prevalence grew faster in low- and middle-income countries than in high-income countries in recent years (1).

DM refers to a pathologic state where the human body cannot efficiently process glucose. Two main types of DM (*i.e.*, type 1 and type 2) can be differentiated. On the one hand, type 1 DM, also known as childhood-onset DM, is characterised by a deficiency of insulin secondary to autoimmune destruction of pancreatic beta cells. On the other hand, type 2 DM, also known as adult-onset DM, which accounts for more than 95% of patients with DM, is characterised by the body inability to use insulin effectively. As insulin plays a key role in regulating blood glucose concentration, DM can cause hyperglycemia. Chronically elevated blood glucose levels harm blood vessels and nerve fibres and lead to end-organ damage (*e.g.*, nephropathy and retinopathy). Further complications include heart disease, arterial hypertension and infections. Thus, DM has serious effects on health-related quality of life (2).

Moreover, the association of DM with malignant tumours has been repetitively described. Patients with type 2 DM are at a greater risk of both developing and succumbing to cancer (3-8). Oxidative stress and DNA damage secondary to hyperglycemia, activation of insulin receptors and insulin-like growth factor receptors *via* hyperinsulinemia resulting in accelerated cell cycle progression, or chronic inflammation have been discussed as possible explanations for the linkage between DM and cancer (7).

From the standpoint of oral health care professionals, the potential impact of DM on various oral diseases, such as xerostomia, decay, periodontal disease, oral candidiasis, or burning mouth syndrome, is of particular significance (9). Recently, the association between DM and oral cancer has also been investigated. It was found that patients suffering from DM showed an increased risk for both precancerous lesions and oral cancer (10-15). However, there is no consensus about the exact molecular mechanisms responsible for this relationship (16).

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Key Words: Diabetes mellitus, glucose metabolism disorder, mouth neoplasms, maxillofacial surgery, epidemiology.

In Austria, DM represents a common ailment. Roughly 600,000 people suffer from DM, or 7%-11% of the total population (17). By comparison, the frequency of head and neck cancer is significantly lower. According to the Austrian Federal Statistical Office, 1,226 people were diagnosed with malignant head and neck tumours in 2018. This accounts for roughly 3% of all newly diagnosed cancer patients in Austria, making it the tenth most common malignancy. Roughly 50% of head and neck cancer are diagnosed after the organ borders have been already broken through. This fact harms both the primary outcome and the 5-year survival rate, which is about 50% (18). In survivors, the postoperative quality of life may be diminished due to the regular need for extensive resection and free flap reconstruction and the sequelae of adjuvant radiotherapy (19). Thus, oral surgery specialists should improve the prevention and early detection of oral cancer.

Against this background, awareness-raising for the possible association between DM and oral cancer among dentists, general practitioners and patients would be desirable to improve prevention and/or early detection of oral cancer. This study aimed to analyse the prevalence of impaired blood glucose levels in patients undergoing maxillofacial surgery and check for the possible linkage between DM and oral cancer. The results should offer a possibility for future cooperation between dentistry, internal medicine and maxillofacial surgery departments.

Patients and Methods

In this retrospective study, we examined the data of all patients who underwent surgery under general anaesthesia at the Department of Oral and Maxillofacial Surgery of the Medical University Graz between January 1, 2018 and December 31, 2019. The data was obtained using the hospital information system openMEDOCS (KAGes Ltd., Graz, Austria).

Patients younger than 40 years and/or pregnant at the time of surgery were excluded from the study. Those who lacked preoperative fasting blood glucose levels were also excluded. Only the initial hospital stay was included if a patient underwent surgery multiple times during the aforementioned period.

The study population was separated into two groups based on the respective diagnosis. On the one hand, individuals who presented with histopathologically confirmed oral cancer made up the cancer group. On the other hand, the control group included all other patients diagnosed with any other condition (*e.g.*, fracture, abscess and dysgnathia).

Since the onset of DM typically occurs about 4-7 years prior to the diagnosis, many cases of DM go unnoticed (2). Therefore, we checked for both diagnoses of DM and abnormal fasting blood glucose levels. Individuals who presented with an already established diagnosis of type 1 or type 2 DM were accordingly listed as patients with DM. We defined impaired fasting glycemia (IFG) as fasting blood glucose levels between 6.1 and 6.9 mmol/l. If patients had not been diagnosed with DM at the time of surgery but had fasting blood glucose levels of more than 6.9 mmol/l, they were regarded as cases with suspected DM-s).

The acquired data was collected in a Microsoft Excel spreadsheet (Microsoft Corp., Redmond, WA, USA) and statistically analysed *via* SPSS Statistics 26.0 (IBM Corp., Armonk, NY, USA). Pearson's Chi-squared test was used to check for differences between the two groups. The significance level was set at 5%.

Ethics approval and consent to participate. The study was conducted according to the Declaration of Helsinki Ethical Principles and Good Clinical Practices guidelines. Participation was voluntary. Approval was granted by the local Ethics Committee at the Medical University Graz (EK-Nr: 1533/2021).

Results

Between January 1, 2018 and December 31, 2019, a total of 1,966 patients underwent surgery under general anaesthesia. After applying the aforementioned exclusion criteria, 573 patients (29.1%) were included in this study. The study population consisted of 227 women (39.6%) and 346 men (60.4%). Their average age amounted to 60 years (range=40-96). One out of four patients (26.5%, n=152) was diagnosed with cancer. Thus, the remaining 421 individuals (73.5%) formed the control group. The portion of males was significantly higher among the cancer group (69.1% *vs*. 57.2%; p=0.01056).

Among oral cancer patients, 13.8% presented with DM (n=21), 25% with IFG (n=38) and 21.1% with DM-s (n=32). By comparison, DM was found in 9% (n=38), IFG in 15.4% (n=65), and DM-s in 12.1% (n=51) of the control group. The rate of a glucose metabolism disorder (GMD; *i.e.*, DM + IFG + DM-s) accounted for 59.9% (n=91) of cancer patients, whereas it added up to 36.5% (n=154) among patients of the control group. This difference was statistically significant (p<0.00001).

In terms of tumour location, no significant difference was observed between cancer patients with GMD and without GMD (p=0.71864). However, sublingual and gingival tumours were the most frequent oral cancer locations in both cancer patients with (33% and 22%, respectively) or without (39.3% and 14.8%, respectively) GMD (Table I).

Regarding the type of cancer, squamous cell carcinoma had a frequency of 93.4% (n=142), thus, making it the most common type. Differences between GMD and non-GMD patients did not reach the level of statistical significance (p=0.51009).

The prevalence of smoking among cancer patients (47.7%, n=72) was significantly higher (p=0.00093) than in the control group (32.3%, n=136; Table II). Within the cancer group, the frequency did not significantly differ between individuals with (46.2%, n=42) or without (49.2%, n=30) GMD (p=0.71414).

Discussion

In 2014, DM affected 422 million people worldwide and accounted for 1.5 million annual deaths, rendering it the ninth leading cause of death at that time (1). The incidence

Table I. *The most frequent tumour locations in patients with and without glucose metabolism disorder (GMD). Differences between normoglycemic and non-normoglycemic patients were not statistically significant.*

	Tumour type				
	Sublingual	Gingival	Lingual	Labial	Other
GMD	30 (33%)	20 (22%)	10 (11%)	9 (9.9%)	22 (24.1%)
Non GMD	24 (39.3%)	9 (14.8%)	7 (11.5%)	4 (6.6%)	17 (27.8%)
Total	54 (35.5%)	29 (19.1%)	17 (11.2%)	13 (8.6%)	39 (25.6%)

of this chronic condition increases rapidly. Recent data from the International Diabetes Foundation (IDF) suggests that as many as 537 million people suffer from DM. The IDF estimates that the disease will affect approximately 643 million people by 2030 and as many as 783 million people by 2045 (20). Diabetic vasculopathy and neuropathy may develop if DM is not properly managed (*e.g.*, with dietary measures, drug therapy and insulin therapy). Thus, DM can potentially exert its effects on multiple organ systems (*e.g.*, renal and cardiovascular systems), which explains why it ranks among the top 10 causes of death in adults (21).

In the field of maxillofacial surgery, oral cancer represents one of the most challenging and life-changing diagnoses. Although multiple specialties (*e.g.*, dentistry, otolaryngology and general medicine) are concerned with regular inspections of the oral cavity, it often takes a long time to recognise a suspicious-looking intraoral lesion as oral cancer. This latency may considerably impact the prognosis since delayed diagnosis results in larger primary tumours and metastases. The 5-year survival rate of approximately 50% for head and neck cancer patients witnesses this intricacy (18).

Multiple authors have proposed an association between DM and cancer (10-14). DM is said to accelerate cancer progression and reduce life expectancy (15). Although the exact pathophysiological mechanism behind this relationship is not fully understood, oxidative stress, hyperinsulinemia and chronic inflammation have been discussed as possible causes (7, 22).

This study demonstrated that the prevalence of any form of GMD was significantly higher in the cancer group than in the control group. Our results correspond to findings in Hungary by Végh *et al*. (14). As opposed to this, Ramos-Garcia *et al*. described that the prevalence of oral cancer among patients with DM did not differ from the general population. However, only patients with an established diagnosis of DM were included in their study (15). Another review by Yan *et al*. also described an association between the risk of head and neck cancer and DM. However, they included only type 2 DM cases and their observations did not reach the level of statistical significance (23).

Tobacco smoking has long been established as a leading causative factor of preventable diseases, including various types of cancer (24). Despite the global endeavour to decrease its prevalence, smoking accounts for approximately 30% of oral cancer deaths globally (25). In our study, the frequency of cigarette smoking was significantly higher (p=0.00093) among cancer patients (47.7%) compared with the control group (32.3%). Differences between individuals with and without GMD were not statistically significant (p=0.31209).

Table II. *Prevalence of smoking among patients in the cancer and control group. Smoking was significantly more prevalent in cancer patients (p=0.00093), thus underlining its role as a pivotal risk factor for oral cancer.*

	Smoking	No smoking	Total
Cancer group	72 (47.4%)	80 (52.6%)	152
Control group	136 (32.3%)	285 (67.7%)	421
Total	208 (36.3%)	365 (63.7%)	573

The vital importance of a timely diagnosis of DM has been demonstrated by Hu *et al*., who conducted a retrospective cohort study (26). They have shown that type 2 DM is associated with significantly higher recurrence rates in oral squamous cell carcinoma patients. They could also observe that the administration of the biguanide metformin resulted in significantly increased 5-year survival rates in these patients.

To facilitate early detection of oral cancer, patients with DM must be instructed to attend mandatory dental appointments annually. They should also be advised to follow a strict oral hygiene routine. According to Akl *et al*., this is especially important since most patients with severe systemic conditions have little knowledge and awareness of the relationship between oral health and their respective systemic condition (27). Thus, providing patients with information about the association between DM and oral cancer should be the foundation for possible prevention programs.

Regarding possible limitations, the intrinsic shortcomings of a retrospective study have to be acknowledged. Moreover, a larger sample size could have been obtained if the

observation period had been extended beyond 2018-2019. However, we deliberately excluded 2020 and 2021 since the ongoing COVID-19 pandemic heavily influenced the number of patients treated at our department.

Conclusion

Early detection and oral cancer prevention should be one of the main goals in the field of maxillofacial surgery. This study showed a higher prevalence of oral cancer in patients with DM. Therefore, apart from dentists, other medical disciplines involved in examining the oral cavity (*e.g.*, general medicine, diabetologist) need to be taught about this association. Furthermore, dentistry and maxillofacial surgery residents should be more aware of patients suffering from dysfunctional glucose homeostasis. Moreover, close interdisciplinary collaboration between maxillofacial surgeons and internists should be expedited against the backdrop of providing optimally adjusted care for inpatients with oral malignancies and glucose metabolism disorders.

Conflicts of Interest

None declared.

Authors' Contributions

DB, DV, AV: Conceptualisation, Methodology, Software DB, MU, AV: Data curation, Writing- Original draft preparation. ZB, ZT: Visualisation, Investigation. NJ, MP, VH, KM: Supervision. ZB, ZT: Software, Validation.: PH, ZN, NR, DB: Writing- Reviewing and Editing.

Availability of Data and Materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

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Received December 6, 2021
Revised January 24, 2022
Accepted February 14, 2022