Clinical and Pathological Examination of Relations between Diabetes Mellitus and Oral Cancer, with Particular Reference to HbA1c-levels

PhD thesis

Dr. Ádám János Végh

Károly Rácz Doctoral School of Clinical Medicine

Semmelweis University

Supervisor: Zsolt Németh, MD, DMD, Ph.D

Official reviewers: János Kis, MD, Ph.D

Mercédesz Orsós, DMD, Ph.D

Head of the Complex Examination Committee: Gábor Gerber DMD, Ph:D

Members of the Complex Examination Committee: István Gera, DMD, Ph.D

Zoltán Rakonczay, D.Sc

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List of Abbreviations

ADA - American Diabetes Association

BMI - Body Mass Index

CGM - Continuous Glucose Monitoring

CT - Computed Tomography

DBS - Dried Blood Spot

DM - Diabetes Mellitus

DNA - Deoxyribonucleic Acid

DPP-4 - Dipeptidyl Peptidase-4

eA1c - Estimated A1C

e.g. - "exempli gratia" = for example

etc. - "et cetera" = and others

EQA - External Quality Assurance

FPG - Fasting Plasma Glucose

GDM - Gestational Diabetes Mellitus

GP - General Practice

HbA1c - Hemoglobin A1c

HPLC - High-Performance Liquid Chromatography

HSV - Herpes Simplex Virus

IDF - International Diabetes Federation

IFG - Impaired Fasting Glucose

IQA - Internal Quality Assurance

IVD - In Vitro Diagnostic

KSH - Központi Statisztikai Hivatal (Hungarian Central Statistical Office)

MODY - Maturity Onset type Diabetes in the Young

MRI - Magnetic Resonance Imaging

MRONJ - Medication-Related Osteonecrosis of the Jaw

NEAK - Nemzeti Egészségbiztosítási Alapkezelő (National Health Insurance Fund)

OGTT - Oral Glucose Tolerance Test

PET-CT - Positron Emission Tomography–Computed Tomography

POC - Point-of-care

SCC - Squamous Cell Carcinoma

SD - Standard Deviations

SGLT - Sodium-Glucose Linked Transporter

T1DM - Type 1 Diabetes Mellitus

T2DM - Type 2 Diabetes Mellitus

TIR - Time-In-Range

VAMS - Volumetric Absorptive Microsampling

WHO - World Health Organization

1. Introduction

1.1. Diabetes Mellitus

Diabetes mellitus (DM) is a metabolic disorder primarily characterized by hyperglycemia. DM is caused by inadequate insulin production, insulin action, or both. In 1999, the *WHO* established a classification that is still valid today, describing the following groups:

1. Type 1 Diabetes Mellitus (T1DM) with Idiopathic and Autoimmune Subgroups. The latter may develop due to a T-cell immune response. The therapy, in this case, is lifestyle awareness combined with intensive insulin therapy. This category accounts for a small proportion of all diabetic cases, about 10%.
2. Type 2 Diabetes Mellitus (T2DM): this category mainly includes overweight patients, usually viscerally obese, with hypertension and dyslipidemia, defined by the metabolic syndrome symptom cluster. The management of this group of diseases is based on a healthy diet and physical activity, supplemented by the administration of antidiabetic drugs. As a result of a generally sedentary lifestyle and poor diet, 80-90% of people with diabetes in the western world have T2DM.
3. Secondary Forms: this group includes pathologies with other causes classified as secondary forms in previous classifications (e.g. drug-induced diabetes or pancreatic disease).
4. Gestational Diabetes Mellitus (GDM) [1]

1.2. Oral Cancer

Oral cavity cancer is one of the most prevalent cancers, particularly in underdeveloped nations and the industrialized world. The most general histology is squamous cell carcinoma (SCC), and alcohol and cigarette use are the primary causative factors. Unfortunately, despite the simplicity of early detection, it is not unusual for patients to present with advanced disease.

1.3. The Link between Diabetes Mellitus and Oral Cancer

It is well-known that there is a definite connection between DM and oral cancer. If we type diabetes mellitus and oral cancer into *Pubmed*, there are almost 1500 results, the first dating back to 1963. It is a well-researched area, most of them stating a connection

between the two. It is important to note that according to most authors, DM is not the primary cause of cancer, especially if it is well treated and the patient uses medication. It is also worth mentioning that poorly managed DM patients generally have worse oral hygiene and poorer knowledge of oral health behaviour.

Recent studies have reported a significant association between oral cancer and diabetes mellitus. Several factors contribute to this relationship, including the high glucose levels characteristic of diabetes mellitus, which can promote cancer cell proliferation and invasion. Furthermore, individuals with diabetes mellitus often have compromised immune systems, making them more susceptible to infections and cancer development.

According to a 2019 systematic review and meta-analysis from *Ramos-Garcia et al.*, patients with DM have a significantly higher chance of developing oral tumours, leukoplakia and erythroplakia. In addition, DM also increases the malignancy risk of various organs, such as the pancreas, liver, colorectum, biliary tract (including bile duct and gallbladder), kidney, breast, ovary, endometrium, urinary bladder, stomach, oesophagus, thyroid, meningioma, multiple myeloma, and non-Hodgkin lymphoma.

Metformin, used in the therapy of DM, is currently highly investigated for its tumour-decreasing effect. However, other medications associated with DM are missing these effects, or their tumour-preventing capabilities are conflicting.

In conclusion, oral cancer and diabetes mellitus are two severe medical conditions with a significant association. Therefore, individuals with DM must maintain reasonable glycemic control and receive regular oral cancer screenings to reduce their risk of developing oral cancer.

2. Objectives

DM is one of the most common chronic metabolic disorders. Our main goal was to research new areas of the field. Although DM is considered a predisposing factor for oral cancer, the literature is still incomplete. The articles usually focus on other types of cancer or cancer in general. In our research, we tried to answer the following questions:

1. Is there a relationship between DM and oral cancer?
2. Does DM have a predisposing role regarding oral cancer?
3. Is the number of DM patients with oral cancer still growing, and how does it compare to the general population?
4. Is there a difference between oral and non-oral cancer patients regarding HbA1c levels?
5. Does HbA1c level affect the prevalence of oral cancer?

3. Results

3.1. Materials and methods

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

This study investigated the link between oral cancer patients, DM and preoperative glycated haemoglobin (HbA1c) levels. In addition, 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 *Semmelweis University Department of Oromaxillofacial Surgery and Stomatology* in Budapest, Hungary. 214 patients were admitted to the *Department of Inpatient Care at Semmelweis University Department of Oromaxillofacial Surgery and Stomatology*. The Semmelweis University Diabetes-Dental Research Group created the study protocol.

We split the participants 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 was collected by the patients who had dentoalveolar surgeries in the clinic (benign tumour surgeries, orthognathic surgeries or other non-malignant maxillofacial surgeries). We collected the following data: sex, smoking and drinking habits, DM diagnosis, and hospitalization reasons. We classified DM patients as those whom a diabetologist had previously diagnosed. Next, we recorded the site of the tumour and its histological type in the individuals diagnosed with oral malignancy. The patients in the control group were recruited for various reasons, including benign tumours, maxillofacial injuries, cysts, and Medication-Related Osteonecrosis of the Jaw (MRONJ). Patients who were under 18 years of age and those with a history of substance misuse were excluded

Next, we determined the patients' fasting blood glucose and HbA1c levels. Measurements were conducted in the morning on an empty stomach by our study staff. We used DCONT Hunor (77 Elektronika Ltd. Budapest, Hungary) for the blood glucose testing. For the HbA1c testing, we used SmartTester® (77 Elektronika Ltd. Budapest, Hungary). 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.

Finally, the team visualized the research findings graphically and then conducted the statistical analysis.

3.1.1.1. 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.

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

Our retrospective research study was conducted at the *Semmelweis University, Department of Oromaxillofacial Surgery and Stomatology, 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 DM or IFG, and cause of hospital admission. In addition, we registered the tumour's location and histological type for patients diagnosed with oral malignancy. Body mass index was calculated as the patient's weight in kg/(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 DM group if an internist previously diagnosed them with DM. IFG was considered for patients with fasting blood glucose levels between 6.1 mmol/L and 6.9 mmol/L. We divided the participants into two groups: those diagnosed with oral malignancy as the experimental/oral cancer group and those without the control group.

All data were stored using Microsoft Excel. In addition, our research group conducted similar studies twice in the past 20 years (1998–2002 and 2012–2015). Therefore, we compared our collected data from this study to the results of these previous studies.

3.1.2.1. Statistical analysis

Data analysis was performed using Prism version 8.4.2 (464) software (GraphPad Software, San Diego, 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.

3.2. Statistics of POC clinical study

A total of 214 people were enrolled in the trial. The oral cancer group comprised 113 individuals (n = 113), while the control group comprised 101 patients *(n = 101)*. The following features describe the cancer group: The mean age was 66,3 years old (range 35-95). 62 men (54.87%) and 51 women were in attendance (45.13%). 39 were smokers (34.1% of the patients), and 74 were non-smokers (65.49%). 30 patients consumed alcohol regularly (26.55%), whereas 83 people abstained from alcohol (73.45%). 32 patients (28.32%) had been diagnosed with DM, while 81 did not disclose a DM diagnosis during anamnesis (71.68%). The control group comprised 45 men (44.55%) and 56 women (55.45%). The mean age was 59,7 years (range 37-85). 15 (14.85%) were smokers, whereas 86 were non-smokers (85.15%). There were 11 patients (10.89%) consumed alcohol regularly, while 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 regarding smoking *(p=0.009)* and alcohol intake *(p=0.003)*. We found no significant differences in gender *(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 that of men in the control group. By comparing DM prevalence between the two groups, we can see that the tumour group had an 8.52% greater prevalence of DM. In light of the intraoral placement of the tumours, we obtained the following outcomes in our investigation: gingiva 30 (26.55%), tongue 26 (23.01%), the floor of mouth 16 (14.16%), lower lip 14 (12.39%), pharynx 11 (9.73%), hard palate 8 (7.08%), soft palate 4 (3.54%) and upper lip 4 (3.54%). The results showed that the blood glucose results of the control group were higher than those of the tumour group we studied.

Twenty individuals (17.69%) had a higher HbA1c level 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. Notably, most smokers and alcoholics in the tumour group did not have DM.

The following findings were made in light of the histological type of the malignant tumours (*n* = 113): SCC (*n* = 104; 92.0%), adenoid cystic carcinoma (*n* = 5; 4.4%), mucoepidermoid carcinoma (*n* = 1; 0.9%), verrucous carcinoma (*n* = 1; 0.9%),

schwannoma with malignant transformation ($n = 1$; 0.9%), and prostate cancer metastasis ($n = 1$; 0.9%).

3.3. Statistics of the retrospective study

Of the 597 patients 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 was 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 tumours 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 tumours 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%, 5/3231), surgical removal of benign tumours (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% of patients (58/323) diagnosed with glucose metabolic disorders, of whom 9.9% (32/323) were with IFG and 8.0% (26/323) with DM. The prevalence of DM and IFG among patients with cancer was 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 $p=0.002185$). Over one-third of the control group were smokers (35.9%, 116/323), which had a statistically significant difference from the oral cancer group (45.3%, 124/274; $p=0.020346$).

4. Discussion

Numerous articles - have already been published on how oral cancer, smoking, DM and alcohol intake - influence each other. Our research team was among the first to identify a strong correlation between DM and malignant oral cancers and MRONJ. Not just from *Hungary* but also data from Austria about the higher incidence of DM in oral cancer patients. This issue is also addressed in the current study. Regarding sex and age, this article explored the association between DM, smoking, alcohol intake, and malignant oral lesions. DM is becoming more prevalent worldwide. In this study, DM was 8.52% more prevalent in the tumour 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 nature of HbA1c level assessment.

Obesity and high glycemic variability were associated with an increased risk of all sites, breast and liver cancer and cancer-specific death in T2D. Oral *Magnesium* supplementation could influence glycemic control in T2DM patients. US study proves that non-obese patients with cancer had higher odds of cancer death. Rising HbA1c and increasing age were associated with increased cancer mortality. We now have moderate-certainty evidence that periodontal treatment using subgingival instrumentation improves glycemic control in people with both periodontitis and DM by a clinically significant amount compared to no treatment or usual care. 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 its synergy among various nutrients and foods rather than in any individual component. There can be a substantial discordance between laboratory and eA1C (continuous glucose monitoring - CGM -estimated HbA1c) 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 result of the metabolic status. The authors would like to highlight that the laboratory HbA1c by a diabetologist in an internal medicine department should make the diagnosis of any metabolic disorder such as DM. The dentist has an essential role in DM care, but further examination and the proper diagnosis are not a role. Oral squamous cell carcinoma

patients with higher preoperative HbA1c levels had more extended hospitalization and worse survival outcomes.

Taking the above into account, at the beginning of our research, we expected to obtain a higher percentage of HbA1c levels in the tumour group compared to the control group. However, to our surprise, the control group had higher instantaneous blood glucose values. Accordingly, we must reassess our current ideas about the relationship between oral cancers and DM. In our opinion, it is not necessarily the higher average blood glucose level that increases the likelihood of developing tumours, but rather its fluctuating nature. Patients with DM may have more extreme blood glucose values, whether too high or too low. Such fluctuations in blood glucose levels can cause healthy cells to become tumorous. Proving this hypotension required close patient control and decades of follow-up, for which the conditions were not present in our current situation.

It is a concern if POC HbA1c is a helpful tool to detect metabolic disorders or track the therapy status. Studies from 2010 show us controversial data on POC instruments for diagnosis: only a few devices meet the acceptable performance criteria, and how the test quality will work in the hands of non-professionals is questionable. The author believes that in a dental office, diagnosis is not an issue of the dentist. However, in a critical prevention stage, if abnormal values are detected, the DM care providers can do further interdisciplinary. In the last decade, the technological change in DM care has been remarkable, as insulin pumps, CGM and blood glucose meters are very accurate, and closed-loop systems play a vital role in treating T1DM care. HbA1c diagnostic tools are also developed significantly, and the accuracy is comparable to laboratory diagnostic tools. From a patient's perspective, these tests are fast and more comfortable as the sample is from finger blood instead of the conservative venous blood sampling. A wide range of studies proved the accuracy of HbA1c machines. Another valuable point of POC machines is 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 and test strips are cheaper, with 3-10 euros per stick on average. This could be a perfect solution to widen access to medical care and help find DM early to eliminate the long-term side effects of DM. Norwegian community pharmacies can 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 study duration and participation in the EQA program were probably too short of implementing all the new procedures for all pharmacies. Ambulatory clinics are testing POC HbA1c testing as a practical solution. Another US-based study shows results that POC and HPLC provide evidence for good concordance between HbA1c done by values < 14% and wide variation for POC HbA1c values >14%. In conclusion, we describe an inexpensive, simple to implement and accurate method for obtaining HbA1c results for remote clinics with good patient acceptance and overcoming the many challenges that have hampered DBS and VAMS blood collection. We believe that in addition to necessary face-to-face consultations, virtual consultations supported by remote HbA1c testing, such as described, will significantly advance diabetes care.

5. Conclusions

In conclusion, in our research, we were able to give the following answers to the questions stated at the beginning of this dissertation.

Our first question was if there is any relationship between DM and oral cancer. Of course, there is a connection between the two. The main goal of our retrospective study was to investigate the proportion of DM patients dealing with oral cancer and those who were not. The results show that in the last 20 years, in the oral cancer group, the rate of DM increased from 14,6 % to 35,8 %, so it more than doubled, while the control group's results increased from 5,6 % to 8,0 %. This proves that DM is generally still on a rising curve and demonstrates that DM patients have a higher risk of being diagnosed with oral cancer.

We were also curious if DM has a predisposing role regarding oral cancer. According to our research, DM rises the chance of oral cancer. DM does not cause oral cancer, but if it is mistreated, it is associated with tobacco use and alcohol consumption; if DM patients' compliance and oral hygiene are insufficient, it can multiply the development of oral cancer.

We also investigated if the number of DM patients with oral cancer still growing, and how it compares to the general population. The number of DM patients is still on the rise. Both of our researches confirmed that the DM ratio in the oral cancer population is higher than in the general population and keeps worsening yearly.

Furthermore, our study investigated also if there is a difference between oral cancer and control patients regarding HbA1c levels. We did not find signinficant differences between the two groups in the average ratio. However, comparing the HbA1c results from higher than 6,9 %, we can state that the ratio in the oral cancer group is more than double that in the control group (6,9 % compared to 15,0 %).

Finally, our studies investigated if POC HbA1c levels can affect the prevalence of oral cancer.

The most important, newly discovered achivements of our studies are the following: in our first study, we found that the tumour group had an 8.52% greater prevalence of DM compared to the control group; a difference which was not statistically 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%. The oral cancer group did not have higher blood glucose levels than those of the control group.

In the retrospective study, we concluded that 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. 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)

Our studies regarding this manner suggest a connection between HbA1c levels and the incidence of oral cancer.

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