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DOKTORI ISKOLA

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

PhD thesis

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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

1.1.1. Definition and Description of 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 [1, 2]. The therapy, in this case, is lifestyle awareness combined with intensive insulin therapy [2]. This category accounts for a small proportion of all diabetic cases, about 10 % [2].
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 [1, 2].
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]

Figure 1. DM Global incidence in 2021 (IDF Atlas 10th Edition)

In 2013, the *ADA* defined its classification, which is similar to the *WHO* classification, but more detailed [3]:

1. T1DM (β-cell destruction, usually leading to absolute insulin deficiency)
   1.1. Immune-mediated
   1.2. Idiopathic
2. T2DM (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)
3. Other Specific Types
   3.1. Genetic defects of β-cell function (e.g. MODY3 dysfunction, mitochondrial DNA dysfunction, etc.)
   3.2. Genetic defects in insulin action (e.g. type A insulin resistance, leprechaunism, etc.)
   3.3. Diseases of the exocrine pancreas (e.g. pancreatitis, neoplasia, etc.)
   3.4. Endocrinopathies (e.g. acromegaly, Cushing's syndrome, etc.))
   3.5. Drug or chemical induced (e.g. vacor, nicotic acid, etc.)
   3.6. Infections (e.g. congenital rubella, cytomegalovirus, etc.)
   3.7. Uncommon forms of immune-mediated diabetes (e.g. "Stiff-man"-syndrome, anti-insulin receptor antibodies, etc.)
   3.8. Other genetic syndromes sometimes associated with diabetes (e.g. Down syndrome, Turner syndrome, etc.)
4. GDM

According to the *International Diabetes Federation* (IDF), DM affects around 420 million people globally and 700,000 people in Hungary [3]. T1DM develops rapidly due to various 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 obesity, a poor diet, and a sedentary lifestyle. Therefore, T2DM therapy is highly dependent on the disease's development. Patients with T2DM have frequently been prescribed biguanides (most commonly metformin), DPP-4 inhibitors (sitagliptin), and SGLT-2 inhibitors (dapagliflozin) [4]. All of these medications are intended to lower blood sugar levels by enhancing the 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 when cells have an insulin output so low that even those with T2DM require insulin supplementation [5].

1.1.2. Diagnosis of Diabetes Mellitus

DM is diagnosed by monitoring fasting or random plasma glucose levels, the Oral Glucose Tolerance Test (OGTT), and/or by monitoring HbA1c values [6, 7]. 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 % [8]. Screening a patient's 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 Fasting Glucose (IFG) level. The HbA1c level indicates the proportion of glycated to non-glycated haemoglobin in the blood. These data inform medical practitioners about patients' average glucose levels over the last 3 months. In addition, it offers the advantage of obtaining information for an extended period and is less affected by transitory circumstances [9]. There are two methods for determining HbA1c levels: laboratory and point-of-care (POC) HbA1c testing. POC is a 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 [8]. 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 [10]. When combined with a comprehensive quality management system, HbA1c testing has been shown to enhance DM treatment [11]. 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. One between 5.7 % and 6.4 % indicates prediabetes and one over 7 % indicates DM.

Chronic hyperglycemia and DM can result in various serious complications, including angiopathy, neuropathy, nephropathy, and retinopathy, and are increasingly linked to the development of malignant tumours, including those found in colon, kidney, liver, endometrial, breast, and pancreatic cancer [12]. In addition, several studies have found that people with DM have an increased risk of oral cancer [13]. Metformin use in people with DM may explain a negative correlation between DM and some types of cancer [14].

1.1.3. Diabetes Mellitus in Hungary

The proportion of people with DM in Hungary is in line with the European average, around 7.5 % -7.7 % [1]. It is difficult to say a punctual number; unfortunately, no accurate register currently exists. Therefore, the data is based on approximations. This estimate is made with the help of the *Hungarian Diabetes Association*, based on the medicines dispensed in Hungary. According to a recent Hungarian study published in *Diabetologia Hungarica*, the scientific journal of the *Hungarian Diabetes Association*, in 2014, 772,000 patients had taken NEAK-subsidised blood glucose-lowering medication, 94 % of whom had T2DM. The analysis from 2001-2014 shows that the prevalence of T2DM has gradually increased, but the rate of increase in recent years slowed down, and the number of newly diagnosed DM patients has decreased. Unfortunately, many patients (17-20 %) can be considered "poorly cooperative patients" as they have been diagnosed with DM but have either not attended an appointment or have not been prescribed antidiabetic medication. It is easy to see from the data that the prevalence of DM increases with age, with a prevalence of T2DM of around 20 % in the population over 60 [70, 71].

This means that 1 in 5 people in this age group are affected, which predisposes to a higher incidence of complications. This data also highlights the importance of the medical team identifying the complications of DM patients as accurately as possible and referring patients to specialist services.

Studies based on Hungarian patients suggest that the increased number of patients with DM may play a significant role in the incidence of oral cancer. In Hungary, oral

examinations of these patients are free of charge at local dentists, university clinics and some private clinics, and the diagnosis of abnormalities and oral complications can be made on time.

Further examinations at specialized clinics can confirm abnormalities detected during these screenings, and treatment can be started and continued.

1.1.4. Most Important Complications of Diabetes Mellitus

Physiological processes can explain the complications of DM. High blood sugar levels in DM can damage the body at the cellular level, with the first site of attack being the walls of small blood vessels, the capillaries. These tiny blood vessels can infiltrate all parts of the body, causing them to malfunction, and as the blood vessels are damaged, the efficiency of the organ is impaired, which can generate obvious symptoms for doctors and patients. It is important to emphasize that the complications of DM are caused by neglect of metabolic status, inadequate cooperation and failure to follow lifestyle guidelines, and genetic and other environmental influences (such as stressful workplace, smoking, alcohol consumption, etc.).

The most important complications of DM, according to IDF Diabetes Atlas (10th edition, 2021), are the following:

- Cardiovascular diseases
- Nerve damage (neuropathy)
- Eye disease (mainly affecting the retina)
- Kidney damage (nephropathy)
- Lower limb amputation

1.2. Oral Cancer

1.2.1. Introduction

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.

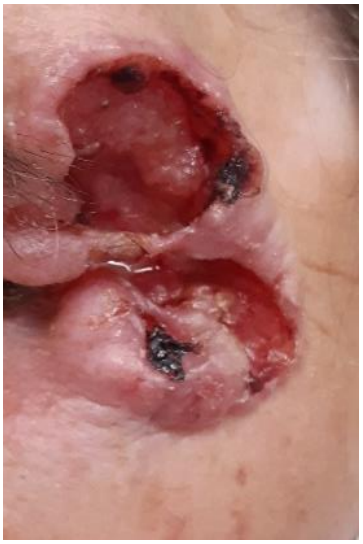


Figure 2. Basalioma in a Patient with Diabetes Mellitus (Source: Personal)

1.2.2. Etiology and Epidemiology

There are expected to be 405,000 new cases of oral cancer worldwide each year, with Sri Lanka, India, Pakistan, Bangladesh, Hungary, and France having the highest rates.[15] An estimated 66,650 new cases are reported in the European Union per year. According to the *American Cancer Society*, there will be approximately 54,540 new oral and pharyngeal cancer cases in the US in 2023, resulting in 11,580 fatalities.[16] The two main causative factors for SCC of the oral cavity are alcohol use and tobacco use. Although hypothesized, the herpes simplex virus (HSV) has not been linked to the etiology of oral cancer.

Hungarian statistics show about 1.5 times as many cancer-related deaths in 2011 as in 1961. Stroke, heart attack, and malignancies of the breast, lungs, and digestive system are currently the leading causes of mortality. Hungary is experiencing a particularly dire scenario.

The rising cancer death rate, already evident in young adults, affects all adults under 64. Between 1948 and 1997, the mortality rate from lung cancer more than doubled, and today it kills almost as many people as tuberculosis did in the past. The age range of 40 to 59 is where the rate of rise is most noticeable. Smoking habits mainly explain this from 20–30 years ago for both men and women, with other factors playing a minor influence. Both sexes can develop the disease, although men have a higher relative risk of dying from lung cancer. Additionally, due to alcoholism being a common condition, there has

been a six-fold increase in mortality from mouth cancer and a considerable increase in the prevalence of liver cancer. Prostate cancer and colon cancer deaths have also risen. Most alarmingly, pancreatic cancer fatalities have increased by approximately 16 times. It is also worth looking at regional differences in cancer mortality. Looking at the mortality rate, the North Great Plain region has the highest value, and the West Transdanubian region has the lowest. The differences between regions are caused by inequalities in socio-economic factors, as the regional coverage and quality of the environment and health care, as well as the different levels of prevention, also play a significant role in cancer incidence. For each region, it can be observed that it is usually a single county that is responsible for the outliers. In the case of the North Great Plain region, for example, Szabolcs-Szatmár-Bereg county has the worst cancer mortality statistics [KSH].

1.2.3. Pathology

More than 90 % of all mouth malignancies are SCCs. Other malignant tumours can develop from the connective tissue, minor salivary glands, melanocytes, lymphoid tissue, or they can metastasize from a different tumour.[17] SCC formation has been linked to several premalignant lesions, such as leukoplakia, erythroplakia, oral lichen planus, and oral submucous fibrosis [18].

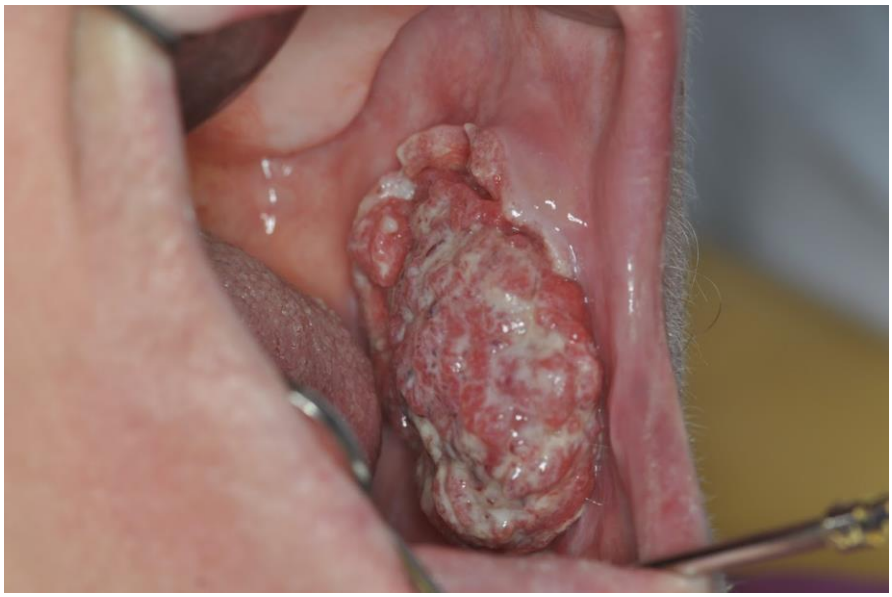


Figure 3. Intraoral SCC (Source: Personal)

Recognizing and treating precancerous conditions is paramount. Therefore, a distinction is made between precancerous lesions and conditions. Laesion is defined as an area of

tissue with altered morphology in which carcinoma may occur more frequently than in normal-appearing mucosa of a similar location. Examples include leukoplakia and erythroplakia. In precancerous conditions, the overall status of the oral mucosa is altered, which is associated with a significantly increased risk of carcinoma. For example, sideropenic anaemia, lichen oris.

The most common precancerous lesion is leukoplakia, an indelible white spot of the oral mucosa larger than 5 mm, which is clinically and pathologically not classified in any other disease group and is not associated with any physical or chemical agent other than smoking.

Histologically we can see a chronic inflammation with hyperkeratinization at the base. It is mainly caused by smoking, although it does not occur in all smokers and is also found in non-smokers, where it is an increased risk.

Several types are known, homogeneous, non-homogeneous (verrucous form), nodular and erythroleukoplakia. Over-infection with Candida albicans is common and requires specific treatment. According to various statistics, the prevalence ranges from 0.57 % to 3.6 %, with 5-6 % malignancy rates, 4.6 % in the simplex form and 28 % in the erosive form. Histopathological examination is essential before treatment. Regular monitoring of the patient is critical. A much worse prognosis than leukoplakia is the appearance of erythroplakia, with epithelial atrophy and marked dysplasia, which may be on the floor of the mouth, in the retromolar area and on the alveolar mucosa of the mandible. At detection, approximately 90 % of histological images show invasive carcinoma or carcinoma in situ.

Precancerous lesions include cheilitis chronica actinica, cheilitis glandularis, cornu cutaneum, keratoma senile and naevus pigmentosus. In addition, there are several precancerous conditions. The most common is lichen oris, which is thought to be due to an autoimmune process. Other conditions are of minor importance, such as sideropenic anaemia, discoid lupus erythematosus, submucous fibrosis, and xeroderma pigmentosum.

1.2.4. Clinical Presentation And Evaluation

Patients with suspected oral cavity cancer must have a thorough head and neck examination. Visual inspection and palpation can provide an accurate sense of the disease's scope, a tumor's third dimension, the presence of bone invasion, or skin disintegration. The tumour's staging, decision-making, and subsequent follow-up can all

benefit from appropriate documentation with drawings and photographic evidence. At the initial encounter, the clinical TNM stage should be noted and changed as the evaluation goes on [17].

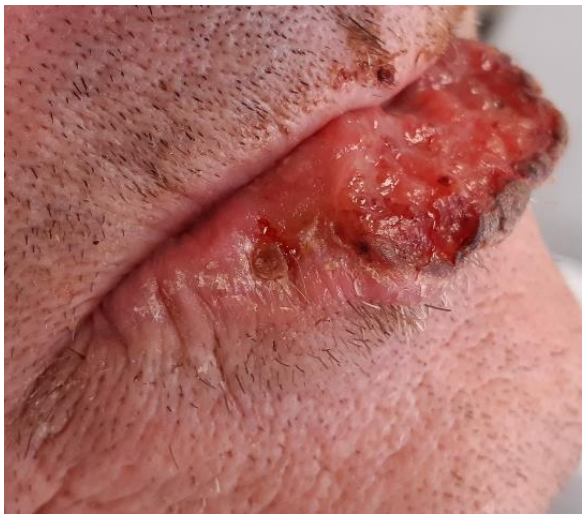


Figure 4. Lower lip cancer (Source: Personal)

The first step of the procedure is a biopsy-based diagnostic. Radiographic imaging is essential for determining the tumour's relationship to the nearby bone and evaluating the local lymph nodes. The preferred technique for assessing bone and neck nodes, particularly early cortical involvement and extracapsular nodal spread, is computed tomography (CT). Because adult marrow is typically replaced by fat, MRI offers complementary information about the extent of soft tissue and perineural invasion. It is also helpful in assessing the extent of medullary bone involvement. It is questionable whether positron emission tomography (PET) should be used in the first evaluation of oral cancer patients because most of them are not at risk for distant metastases. Due to its user-friendliness and relatively straightforward architecture, the TNM system (Table 1., [72]) is the most extensively used prognostic system. Clinical staging for oral cavity malignancies considers the neck, the original tumour, and any potential distant metastases. TNM stage grouping for the tumour is made possible by this information [19]. The size of the tumour and the infiltration of deep structures are the fundamental factors in staging the leading site. Typically, lymphatic expansion into the neck happens in an organized, progressive manner that is predictable. The design of the neck dissection for patients with oral cancer can be affected practically by understanding the patterns of nodal metastases. The patient at risk of developing metastases to levels I to III has a clinically

negative neck. Level IV skip metastases do happen, particularly in anterior tongue carcinoma. Even in patients with clinically positive neck, metastatic disease reaching level V is highly uncommon (1 %). Of all oral malignancies, oral tongue tumours have the highest propensity to spread to the neck, and tumour thickness is a crucial indicator of the likelihood of nodal metastasis [20].

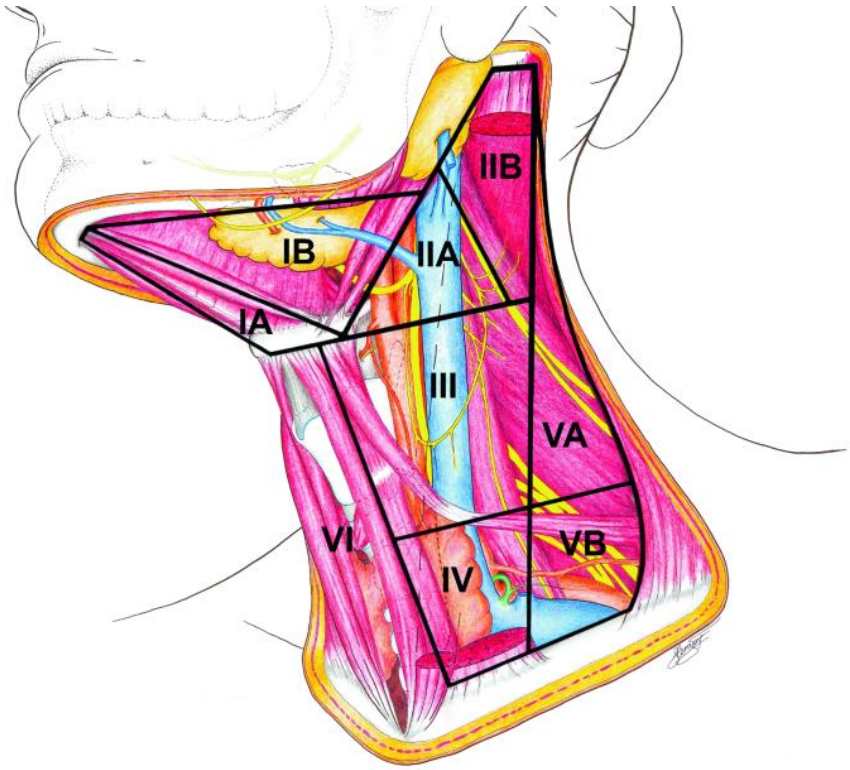


Figure 5. Surgical neck areas [21]

Table 1. TNM classification of cancers of the oral cavity (UICC [72])

TNM classification of carcinomas of the oral cavity	
T	**Primary Tumor**
TX	Primary tumours cannot be assessed
T0	No evidence of a primary tumour
Tis	Carcinoma in situ
T1	Tumour 2 cm or less in greatest dimension
T2	Tumour more than 2 cm but not more than 4 cm in greatest dimension
T3	Tumour more than 4 cm in greatest dimension
T4a (lip)	Tumour invades through cortical bone, inferior alveolar nerve, the floor of the mouth, or skin (chin or nose)
T4a (oral cavity)	Tumour invades through cortical bone, into deep/extrinsic muscle of the tongue (genioglossus, hyoglossus, palatoglossus, and styloglossus), maxillary sinus, or skin of the face
T4b (lip and oral cavity)	Tumour invades masticator space, pterygoid plates, or skull base; or encases internal carotid artery
N	**Regional Lymph Nodes**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2	Metastasis as specified in N2a, 2b, 2c below
N2a	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph node more than 6 cm in the greatest dimension
M	**Distant Metastasis**
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

1.2.5. Treatment

The preferred course of treatment for oral carcinoma is surgical resection. Resection enables precise pathologic staging, providing details about the margins' condition, the tumour's extent, and histopathologic features. This information can then guide further care based on evaluating risk against benefit. For particular purposes in locoregionally advanced malignancies, adjuvant radiation may be administered in combination with or

instead of chemotherapy. A multidisciplinary team is necessary to guarantee a successful conclusion (stomato-oncological tumour board). When choosing a course of treatment for a particular patient, several criteria are considered. Physiologic age, comorbid diseases (such as cardiovascular status), lifestyle factors (such as smoking or alcohol use), surgical resectability, and patient expectations should all be considered when determining the risk of treatment-related problems.

Reconstruction after ablative cancer surgery restores form and function. Primary closure, skin grafts, or substitutes can generally restore surgical flaws after early-stage tumour removal. However, expert reconstructive surgeons must reconstruct more sophisticated flaws following advanced tumour removal [22, 23]. Free flaps can rebuild bone and soft tissue. Radial forearm osteocutaneous, iliac crest, and scapula-free flaps are other composite microvascular flaps. Microvascular free flap repair is reliable and low-morbidity [24]. Reconstructing significant surgical flaws has improved oncologic outcomes in locally advanced cancer patients by allowing more complete resections [25]. If surgical skill is unavailable or the patient is not a candidate for microvascular restoration, pedicled myocutaneous flaps such as pectoralis major, latissimus dorsi, or trapezius flaps are reliable alternatives.

Patients with a high risk of locoregional recurrence should get postoperative adjuvant care. Patients with significant initial tumours (pT3 or pT4), substantial nodal disease (pN2 or pN3), metastases to nodal levels IV or V, positive surgical margins, lymphovascular invasion, perineural invasion, and extracapsular spread are included in this cohort. External beam radiation therapy has traditionally been used for postoperative adjuvant treatment, and dosages of 66 to 70 Gy produce effective locoregional control [26, 27]. Concurrent chemoradiation is best performed in facilities with the necessary equipment and experience because it can cause severe morbidity.

1.2.6. Outcomes Of Treatment

Oral cancer patients have a significant risk of locoregional and secondary malignancies but a low chance of distant recurrence [28]. Therefore, early diagnosis requires a thorough clinical examination and a high suspicion of a second head and neck primary, which occurs 4-7 % of the time [29]. Due to the higher likelihood of treatment failure and second primaries, these patients must control lifestyle risk factors like smoking and consuming

alcohol [30]. Chemoprevention is ineffective. Thus close follow-up is the best secondary prevention method [31]. Baseline imaging examinations are usually done 3–6 months after therapy and as needed for clinical suspicion. Smokers benefit from chest imaging. Speech and swallowing rehabilitation, thyroid-stimulating hormone monitoring if the neck has been radiation-treated, and dental exams are further auxiliary treatments.

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 [32].

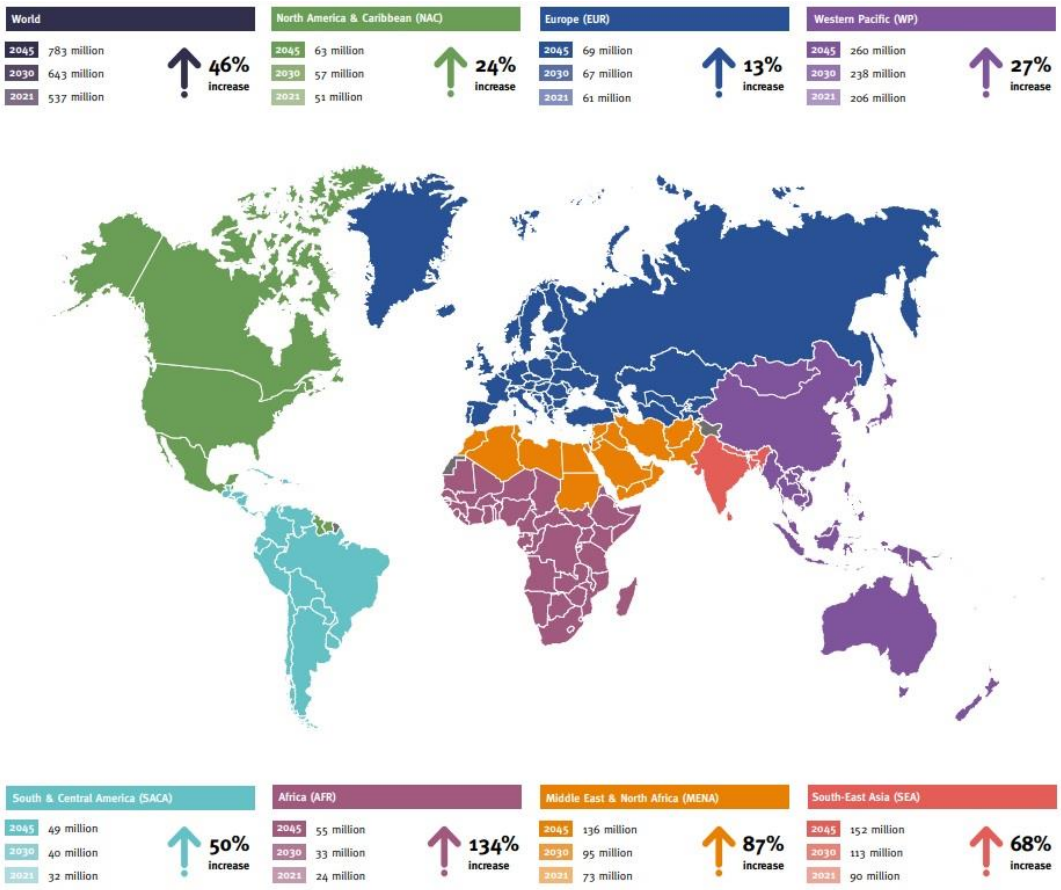


Figure 6. Expected Growth of Diabetes Mellitus 2021-2045 (IDF Atlas 10th Edition)

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 [33]. 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 [34].

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 [35].

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:

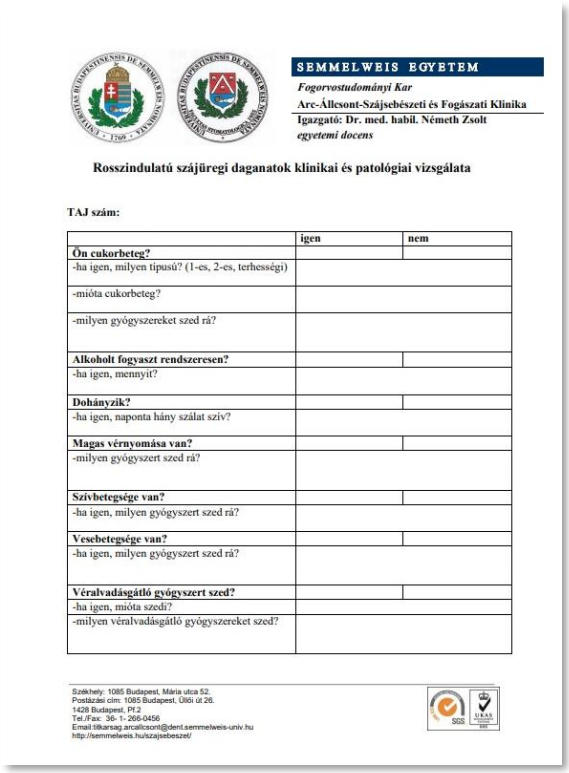
1. Is there a relationship between DM and oral cancer?
2. Does DM have a predisposing role regarding oral cancer?
3. Is the number of DM patients with oral cancer still growing, and how does it compare to the general population?
4. Is there a difference between oral and non-oral cancer patients regarding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

3. Materials and methods

3.1. 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 maxillofacial and/or dentoalveolar surgeries in the clinic (benign tumour surgeries, orthognathic surgeries or other non-malignant maxillofacial surgeries, etc.). 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



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Igazgató: Dr. med. habil. Németh Zsolt
egyetemi docens

Rosszindulatú szájüregi daganatok klinikai és patológiai vizsgálata

TAJ szám:

	igen	**nem**
Ön cukorbeteg?		
-ha igen, milyen tipusú? (1-es, 2-es, terhességi)		
-mióta cukorbeteg?		
-milyen gyógyszereket szed rá?		
Alkoholt fogyaszt rendszeresen?		
-ha igen, mennyit?		
Dohányzik?		
-ha igen, naponta hány szálat szív?		
Magas vérnyomása van?		
-milyen gyógyszert szed rá?		
Szívbetegsége van?		
-ha igen, milyen gyógyszert szed rá?		
Vesebetegsége van?		
-ha igen, milyen gyógyszert szed rá?		
Véralvadásgátló gyógyszert szed?		
-ha igen, mióta szedi?		
-milyen véralvadásgátló gyógyszereket szed?		

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http://semmelweis.hu/szajsebeszet/

Figure 7. A simplified anamnesis questionnaire to be completed by patients before each visit (Source: Personal)

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.

Figure 8. and 9. SmartTester by 77 Elektronika Kft. and blood sampling with a disposable spear (Source: Personal)

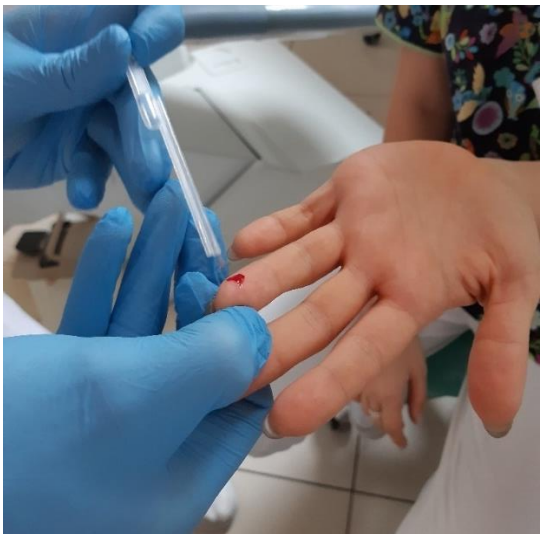

Figure 10. and 11. Determination of instantaneous blood glucose level and taking a drop of blood by a pipette (Source: Personal)

Figure 12. and 13. mixing blood with reagent solution and applying the solution to the measuring cassette (Source: Personal)

Figure 14. The SmartTester showing the result (Source: Personal)

3.1.1. 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.

During the collection of data, we usually checked the anamnestic sheet with the patients once more, so missing information was rare. In those cases, if that data was important, and would have distorted the end reasults, we excluded the patient from the research.

3.2. 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 [36]. 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 [37] and 2012–2015 [38]). Therefore, we compared our collected data from this study to the results of these previous studies (Table 5.).

3.2.1. 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.

3.3. Ethical approval

Both studies were conducted by the Declaration of Helsinki Ethical Principles and Good Clinical Practices and were approved at each site by the Ethical Committee of Semmelweis University (Budapest, Hungary). Ethical Approval Number: SE-RKEB 204/2018.

4. Results

4.1. 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 %). In the results, in line with the international guidelines, we considered those people alcoholic, who self-reportedly regularly, but at least once a week consumed alcohol. 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 %). (Table 2). Table 3 contains the average HbA1c levels in different patient groups. The results showed that the blood glucose results of the control group were higher than those of the tumour group we studied.

Table 2**.** 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 %)		
	Upper lip	4 (3.54 %)		
	Lower lip	14 (12.39 %)		
	Tongue	26 (23.01 %)		
	Soft palate	4 (3.54 %)		
	Floor of mouth	16 (14.16 %)		

Table 3**.** 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

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. (see Table 4.).

Table 4. 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 %)	
Smoker	Non-DM	33	(29.2 %)	10	(9.9 %)	0.142
	DM	6	(5.3 %)	5	(4.95 %)	
Alcoholic	Non-DM	24	(21.2 %)	5	(4.95 %)	0.031
	DM	6	(5.3 %)	6	(5.94 %)	

The following findings (Table 5.) 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 %).

Table 5. Histological classification of the malignant tumours.

	(*n*)	(%)
SCC	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
Malignant schwannoma	1	0.9

4.2. 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; $p=0.020346$).

5. Discussion

Numerous articles - have already been published on how oral cancer, smoking, DM and alcohol intake - influence each other [39-45]. Our research team was among the first to identify a strong correlation between DM and malignant oral cancers [46-49] and MRONJ [50]. Not just from *Hungary* but also data from Austria about the higher incidence of DM in oral cancer patients. [51] 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 [51]. 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 T2DM [52]. Oral *Magnesium* supplementation could influence glycemic control in T2DM patients [53]. 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 [54]. 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 [55]. 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. [56] 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 diagnosis and medical care of any metabolic disorder, such as DM, should be managed by a specialised interal medicine department. The dentist has an essential role in DM care, but further examination and the proper diagnosis are not a role [57]. Oral squamous cell carcinoma

patients with higher preoperative HbA1c levels had more extended hospitalization and worse survival outcomes [58].

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 hypothesis required close patient control and decades of follow-up, for which the conditions were not present in our current situation. [73, 74, 75]

Table 6. 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 %

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 [59]. 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 [60, 61]. 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 [62]. 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 [63]. Ambulatory clinics are testing POC HbA1c testing as a practical solution [64]. 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 % [65]. 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 [66].

5.1.1. Limitations of the POC-study

The investigation has several limitations, such as comparing the POC HbA1c data with a high-performance liquid chromatography (HPLC) dataset.

In the future, the postsurgical complications regarding the presurgical metabolic data can be further investigated in cooperation with the internationally recommended thresholds.

6. 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.

7. Summary

Our studies aimed to investigate the link between preoperative glycated haemoglobin (HbA1c) levels of oral cancer patients and control patients. We highlighted the importance of point-of-care HbA1c measurements in oral cancer patients.

In our main study, 214 patients admitted to the *Department of Inpatient Care at Semmelweis University's Department of Oromaxillofacial Surgery and Stomatology* between September 1, 2020, and May 21 2021; individuals, who had undergone maxillofacial surgery under general anaesthesia, were included in the study. We also 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).

Our POC study showed a significant difference between the oral cancer group and the control group regarding 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 tumour group had an 8.52 % greater DM prevalence, which was insignificant. Twenty individuals in the oral cancer group (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 %, meaning their metabolic level was poor. The oral cancer group did not have higher blood glucose levels than the control group. From our retrospective study, we learned 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; of these, 61.1 % had T2DM, 34.2 % had impaired fasting glycemia, and only 4.7 % had T1DM. 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).

Our primary research found that elevated HbA1c level (>6,9 %) is more common in the oral cancer group. Furthermore, our retrospective study showed an increase in the number of DM patients in the oral cancer group. These data show a clear link between DM and

oral cancer. These facts make point-of-care HbA1c measurement an important preventive, diagnostic tool in the dental office.

8. References

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