

# Characteristics of dental care for diabetic patients

Ph.D. Thesis

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Budapest  
2018

## **1. Introduction**

Diabetes affects more than 300 million people worldwide – 750.000 people in Hungary - according to the latest statistics of the International Diabetes Federation (IDF) and the Hungarian Diabetes Association (MDT). According to these data every 10th patient in Hungary arriving for a dental visit has diabetes or increased fasting glucose (IFG) level. Diabetic patients are considered to be a risk group for dental complications. Diabetic patients might have a higher risk to have periodontal problems, caries, oral diseases, also the incidence of oral cancer is statistically higher in the diabetic population compared to the non-diabetic group. The topic of my Ph.D. thesis is a new research trend in international level, motivated by the increased number of patients with diabetes. Hungary is leading in the morbidity and mortality in oral cancer and the incidence of type 2 diabetes is constantly elevating. During regular diabetes treatments, oral screening should be a core element of proper diabetes care.

The goal of our project – which was launched in 2015-, is to help and improve with our screening and experimental results the dental care of diabetic patients and to help the improvement of their quality of life.

## **2. Types of diabetes**

### *Type 1 diabetes*

This type of diabetes is an autoimmune disease when the immune system attacks the insulin-producing beta cells in the pancreas, the body can produce little or no insulin, which causes relative or total insulin deficiency.

### *Type 2 diabetes*

The most common type of diabetes is type 2, which consists the 90 % of all population of diabetes. In this type of diabetes, the hyperglycemia is caused by the disturbances in insulin production or by insulin resistance, therefore insulin can not produce its effect. The insulin sensitivity of cells is decreasing, insulin resistance will be developed, therefore insulin will be ineffective resulting in the overproduction of insulin. The elevated level of insulin can balance the higher blood glucose level in the beginning, but in the long term, the insulin resistance will be worse.

### *Gestational diabetes*

Gestational diabetes (GDM) is a metabolic disorder occurring during pregnancy.

### **2.1. Complications of diabetes**

The complications of diabetes can be explained by physiological processes. Chronic elevation of blood glucose level leads to damage of blood vessels called angiopathy.

The most common complications:

1. cardiovascular complications
2. diabetic eye disease, retinopathy
3. nephropathy
4. neuropathy
5. pregnancy-associated complications
6. oral health complications

### **3. Aims**

**3.1.** Comparative epidemiological studies to investigate the relationship between oral cancer and diabetes.

**3.2.** Investigation of the effect of local anesthetics on the release of noradrenaline in diabetes, in rat experiments.

**3.3.** Establishment of diabetes-specific dental working-group.

**3.4.** Development of an interdisciplinary protocol with the cooperation of the Hungarian Diabetes Association. Guidelines of dental screening in the treatment of diabetic patients.

#### **3.1. Comparative epidemiological studies to investigate the relationship between oral cancer and diabetes**

We examined the incidence of diabetes mellitus (DM) and impaired fasting glucose (IFG) in the oral cancer group. We were interested in the prevalence of diabetes or IFG was risen among the local Hungarian population in the last 15 years compared with the previous data. We conducted a retrospective research study in the inpatient ward of the Semmelweis University Department of Oral and Maxillofacial Surgery, Budapest, Hungary. We examined patients who were diagnosed with histologically confirmed malignant oral tumors. The examination period was between the 1st of January, 2012 and 31st of December, 2015. These results were compared to an earlier study that was

conducted in the same department between the 1st of January, 1998 and 30th of June, 2002.

### 3.1.1. *Methods*

We processed the data of 610 patients (435 males and 175 females) in the first interval and the data of 758 patients (400 male and 358 female) in the second interval. All patients were diagnosed with histologically confirmed malignant cancer. Based on these histological data, we confirmed 606 cases among the 610 and 749 cases among the 758 were squamous cell carcinomas, while the remainder consisted of adenocarcinomas. The average age of the patients from the previous study was 56 years (range=36-85), whereas the average age of the patients in the follow-up study was 64 years (range =12-92). The control group in the first research interval was formed by 574 patients (351 male, 223 female). Their average age was 51 years (range=32-79). The control group in the second study interval was formed by 534 patients (318 male, 216 female) with an average age of 53 years (range=30-94). The patients of the control group in both study intervals volunteered for stomato-oncological screening and found symptom- and cancer free.

### 3.1.2. *Results*

*Table 1. – Prevalence of IFG and diabetes among patients diagnosed with oral cancer*

	ORAL CANCER GROUP		CONTROL GROUP	
	1998-2002	2012-2015	1998-2002	2012-2015
DM	14.6%	25.9%	5.6%	10.3%
IFG	9.7%	20.6%	5.5%	10,5%

**Table 2.** – Oral cancer locations among patients with and without diabetes examined between the years 2012 and 2015.

	Labial tumor	Lingual tumor.	Sublingual tumor	Gingival tumor.	Other tumor	TOTAL
NON DM	21.7% (122)	18.5% (104)	22,1% (124)	30.2% (170)	7.5% (42)	562
DM	34.7% (68)	21.4% (42)	13.3% (26)	19.4% (38)	11.2% (22)	196
TOTAL	25% (190)	19.3% (146)	19.9% (150)	27.4% (208)	8.4% (64)	758

These results indicated that 46.5% of the oral cancer group had a metabolic disorder (DM+IFG). In the tumor-free control group of 534 patients, 10.3% (55 patients) had DM and 10.5% (56 patients) IFG. In the control group, 20.8 % (111) had a glucose metabolic disorder. The rate of metabolic disorder in the oral cancer group was significantly higher than in the control group ( $P<0.05$ ).

Upon comparing the present study to the data that we collected 14 years earlier, we found that the rate of diabetes increased from 14.6 % to 25.9%, while the rate of IFG increased from 9.7% to 20.6% ( $P<0.05$ ). Among the tumor-free control group, the rate of DM climbed from 5.6% to 10.3%, as did IFG from 5.5% to 10.5%, which was statistically significant ( $P<0.05$ , Table 1).

Based on the statistical analysis the prevalence of patients with glucose metabolic disorders (IFG+DM) increased from 24.3% to 46.5 % among patients with oral cancer. In control groups, this data increased from 11.1 to 20.8% ( $P< 0.05$ , Table 1). The most common cancer locations in the non-diabetes oral cancer group were gingival cancer (30.2%), and sublingual malignant tumors (22.1%). The most frequent types of tumors among patients with diabetes were labial and lingual cancers (34.7% and 21.4%, Table 2).

### **3.1.3. Discussion**

Malignant tumors and DM are serious public health issues worldwide. This phenomenon is especially prevalent in Hungary, as this country ranks first in oral cancer morbidity and mortality in Europe. As diabetes is a risk factor for oral complications, annual oral screening needs to be highlighted in diabetes care guidelines. We would like to draw attention to the rapidly increasing number of oral cancer patients with glucose metabolism disorders and highlight the importance of regular stomato-oncological screening and interdisciplinary cooperation between medical professionals in the fields of type 2 diabetes and oral cancer.

## **3.2. Investigation of the effect of local anesthetics on noradrenaline release in experimental diabetes, in rat experiments.**

In our studies we have compared the effects of lidocaine and articaine, a widely used anesthetics in dental practice, on the resting and axonal stimulation-evoked release of noradrenaline ([NA) in the prefrontal cortex and spinal cord slices prepared from non-diabetic and streptozotocin-induced diabetic rats.

### **3.2.1. Methods**

#### *Streptozotocin (STZ) treatment*

Rats were injected (i.p.) with STZ (60 mg/kg) dissolved in distilled water (2.5 ml/kg). The age-matched control rats were injected with an equal volume of distilled water. Rats were considered diabetic if the blood glucose level was higher than 14 mmol/l.

#### *Tissue preparation*

After 9 weeks of treatment with STZ, the animals were decapitated, the frontal cortex and spinal cord slices (400 µm thick) were prepared with a McIlwain slicer, and placed in ice-cold Krebs solution and bubbled with carbogen (95% oxygen + 5% carbon dioxide).

#### *Measurement of [<sup>3</sup>H]-Noradrenaline release*

The slices were incubated with Levo-[7-<sup>3</sup>H]noradrenaline ([<sup>3</sup>H]NA, 5 µCi/ml, sp. activity: 14.8 Ci/mmol) for 45 min at 37 °C in 1 ml Krebs solution (NaCl 113, KCl 4.7, CaCl<sub>2</sub> 2.5, KH<sub>2</sub>PO<sub>4</sub> 1.2, MgSO<sub>4</sub> 1.2, NaHCO<sub>3</sub> 2.5, glucose 11.5, ascorbic acid 0.3, Na<sub>2</sub>EDTA 0.03

mmol/l) bubbled with carbogen. After loading, the tissue was transferred to a microvolume (100 $\mu$ l) perfusion system and was perfused (Gilson peristaltic pump) at a rate of 0.5 ml/min for 60 minutes with carbogen bubbled Krebs solution. The effluent used for washing was discarded. During the experiments, the tissue was stimulated at the 3rd and 13th fractions, via platinum electrodes (built in the chamber) using a Grass S88 stimulator. Stimulation parameters were frontal cortex: 20 V, 2 Hz, 2 ms impulse duration, 90 sec, spinal cord: 40 V, 3Hz, 1 ms impulse duration, 80 sec. Anesthetics were introduced to the chamber before the second stimulation at the 6th fraction. During the continuous perfusion 3 minutes, fractions were collected and their radioactivity was measured by liquid scintillation method (Packard TR 1900). At the end of the experiment, the radioactivity of the tissue was measured. The amount of the released NA was expressed as the fractional release (FR% ), the radioactivity of the fraction was calculated as a percentage of the total tritium content of the tissue at the onset of the collection period.

### **3.2.2. Results**

*Uptake and release of [3H]NA measured in the prefrontal cortex (PFC) and spinal cord slices prepared from non-diabetic and diabetic rats.*

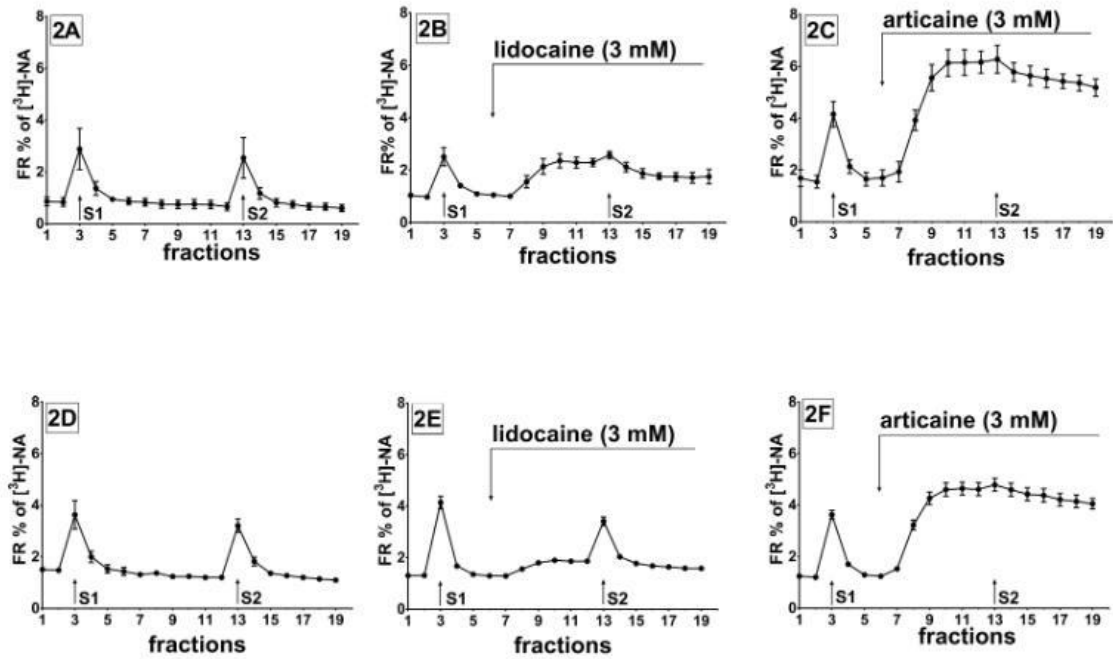
The uptake and the resting release of [<sup>3</sup>H]NA in PFC slices of diabetic rats, were significantly higher compared with those of non-diabetic rats. However, there was no significant difference in the amount of NA released by axonal stimulation. When we have compared non-diabetic and diabetic rats, there was no significant change in the uptake, in the resting and stimulation-evoked release of NA in spinal cord slices.

*Effects of articaine and lidocaine on [<sup>3</sup>H]-NA release from PFC and spinal cord slices prepared from non-diabetic and diabetic rats*

In non-diabetic PFC slices lidocaine at a concentration of 3 mM reduced the stimulated evoked release and fully inhibited it at a concentration of 10mM. At a concentration of 3mM, articaine inhibited significantly the stimulation-evoked release and totally inhibited it at a concentration of 10 mM.

At 3 mM and 10 mM lidocaine concentration, the resting release in non-diabetic rats was increased about 3 and 5 fold. Articaine at the 0.3 mM concentration already induced a

significant 1.6-fold increase in resting release measured in non-diabetic rats, at 3 mM and 10 mM concentration a significant enhancement (4 and 15 fold) was measured. 3 mM lidocaine and 3 mM articaine increased the resting release in PFC slices of non-diabetes and diabetes rats, the enhancement was not significantly different in the preparations of two types of animals ( Figure 1.)

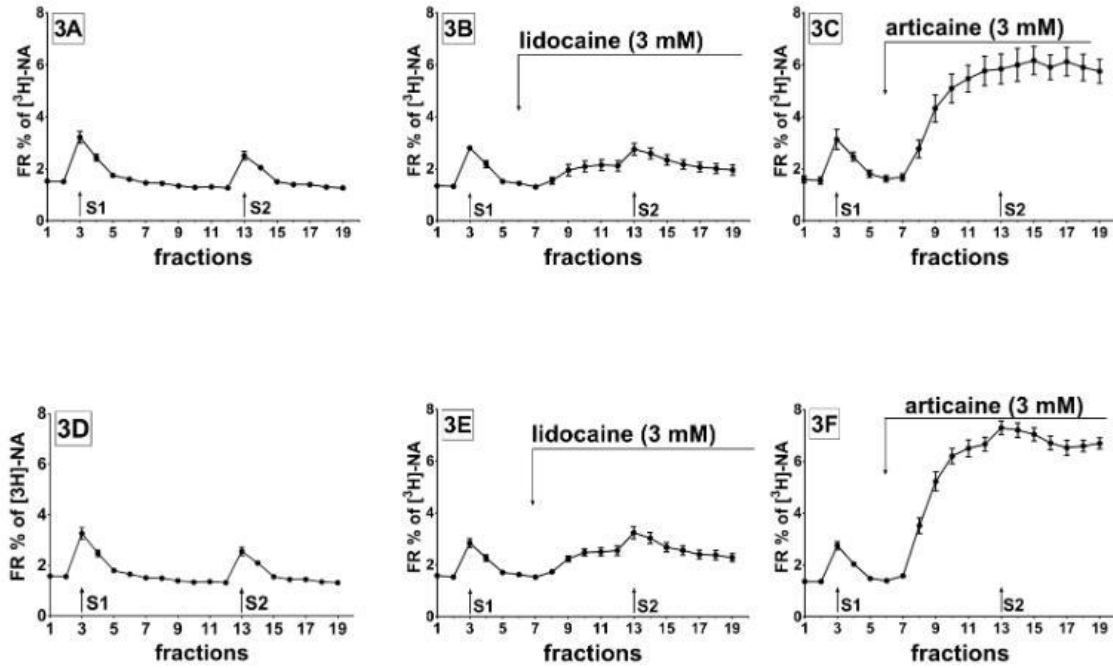


**Figure 1.** Effects of lidocaine (B and E) and articaine (C and F) on the fractional release of  $[^3\text{H}]$ noradrenaline (FR% of  $[^3\text{H}]$ NA) in prefrontal cortex slices prepared from non-diabetic (A, B, C) and diabetic (D, E, F) rats. A and D show control experiments. The slices were stimulated twice ( $S_1$  and  $S_2$ ), as indicated, stimulation parameters were: 20V, 2 msec, 2Hz, 90 sec ( $\Sigma$ 180 shocks). Data represent Mean  $\pm$  SEM, the number of experiments: 6. The administration of local anesthetics from the 6<sup>th</sup> fraction is indicated. The release of  $[^3\text{H}]$ NA was increased by both local anesthetics in non-diabetic and diabetic preparations and was highly significant, ( $P < 0.05$ ).



In spinal cord slices (Figure 2.) 3 mM lidocaine and 3 mM articaine significantly increased the resting release, and their effects on the release of NA from slices prepared from non-diabetic and diabetic animals have not differed.

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**Figure 2.** Effects of lidocaine (B and E) and articaine (C and F) on the fractional release of [ $^3\text{H}$ ]noradrenaline (FR% of [ $^3\text{H}$ ]NA) in spinal cord slices prepared from non-diabetic (A, B, C) and diabetic (D, E, F) rats. A and D show control experiments. The slices were stimulated twice ( $S_1$  and  $S_2$ ), as indicated, stimulation parameters were: 40V, 1 msec, 3Hz, 80 sec ( $\Sigma 240$  shocks). Data represent Mean  $\pm$  SEM, the number of experiments: 6. The administration of local anesthetics from the 6<sup>th</sup> fraction is indicated. The release of [ $^3\text{H}$ ]NA was increased by both local anesthetics in non-diabetic and diabetic preparations and was highly significant, ( $P < 0.05$ ).

### **3.2.3. Discussion**

In dental care and during spinal and epidural anesthesia, the neurons are exposed to relatively high concentrations of local anesthetics that diffuse directly into the tissue and beside their therapeutical action may cause adverse effects. In epidural anaesthesia and dental treatments 1.5-2% lidocaine (55.2-69.25mM) or 1-4 % of articaine (31.41-124.67 mM) are used.

In our experiments, there was no difference in the axonal stimulated NA release in PFC and spinal cord slices prepared from non-diabetic and diabetic rats. These findings indicate that there is no impairment in nerve conduction. The uptake and resting release of NA were higher in PFC slices prepared from diabetic rats but no change was observed in preparations obtained from the spinal cord. The inhibitory effect of local anesthetics, lidocaine, and articaine on the release of NA from nerve terminals in response to axonal activity and the increase in resting release indicate a  $\text{Na}^+$ -channel - or  $\text{K}^+$  channel-dependent action. The inhibition of axonal stimulated release results in the blockage of conduction and numbing of pain, and the enhancement of resting release may produce adverse effects. Using the same concentration of lidocaine and articaine, the effect of articaine on the increase of resting NA release was more pronounced.

When the therapeutic efficacy of articaine was compared to that of other local anesthetics (lidocaine, prilocaine, and chlorprocaine), the studies failed to show any evidence of clinical advantages of any anesthetic over another. In clinical practice, the concentrations used in our experiments can easily be reached inhibiting both the  $\text{Na}^+$  and  $\text{K}^+$  channels. The inhibition of  $\text{K}^+$  channels is dominant in neurotoxicity, the release of large amounts of transmitters, including NA and glutamate, into the extracellular space, where NA metabolites (DOPAL, DOPEGAL) and glutamate itself could be neurotoxic. In this respect, articaine has a thiophene ring with high solubility, which may confer a potential risk for some patients, neurosensory disturbances associated with 4% formulations of articaine used in dentistry may have occurred. Comparing with other local anesthetics, articaine displays negligible cardiotoxic effects. Studies have shown, the diabetic patients with neuropathic pain, treated by local anesthetics for a shorter or longer period of time undergoing oral surgery or dental care, may have more chance for neurotoxicity, therefore the use of appropriate dosage of articaine is essential.

### **3.3. Establishment of diabetes-specific dental working-group**

In 2015 we organized a working group in the Semmelweis University Department of Prosthodontics with the leadership of Prof. Dr. Péter Hermann and with the participation of Dr. Márta Ujpál and Dr. Dániel Végh. Our task is to investigate the oral complications in diabetic patients and to provide them the proper care.

#### **3.3.1. Postgraduate course**

In 2016 I lectured in 4 postgraduate courses of the Hungarian Medical Chamber – Dental Faculty's Postgraduate Series, in 4 different Hungarian cities (Budapest, Miskolc, Győr, Szekszárd) about the correlation of diabetes and oral complications, and the diabetes-related emergencies in the dental office.

#### **3.3.2. Hungarian Diabetes Association**

The Hungarian Diabetes Association is supporting this research project since the beginning. There was an agreement between Prof. Dr. Péter Kempler (President of the Hungarian Diabetes Association) and Prof Dr. Péter Hermann (President of the Dental Faculty of the Hungarian Medical Chamber ), that we are helping each other to make oral health complications a core issue of the diabetes care guidelines.

As part of the agreement, we are presenting our newest research results in the Annual Meetings (past: 2017, 2018) of the Hungarian Diabetes Association.

### **3.4. Development of an interdisciplinary protocol with the cooperation of the Hungarian Diabetes Association. Guidelines of dental screening in the treatment of diabetic patients.**

Interdisciplinary meeting („Associations between diabetes mellitus and cancer”) was held in the Aeskulap Academy in 2017 organized by MOTESZ, with the participation of the following medical associations: Hungarian Association for Cranio Maxillofacial Surgery, Hungarian Diabetes Association Society of Hungarian Urology, Hungarian Surgical Society, Hungarian Society of Oto-Rhino-Laryngology, Head and Neck Surgery

### **3.4.1. Guidelines**

1. Diabetes is a major health issue, which affects directly 750.000 people in Hungary, and approximately 1.5 million people are living with metabolic disorders with increased blood glucose level.
2. In certain localizations(breast, endometrium, kidney, bladder, pancreas, oral cavity) the prevalence of tumors is higher in the diabetic population compared with the non-diabetic population.
3. The association between diabetes and cancer in different locations are highlighted by a great number of international studies. The most important tasks for the national health system is to provide the proper care and support the prevention.
4. Proper nutrition and abandonment of bad habits (smoking, regular alcohol consumption), regular medical check-ups and proper medical care are necessary.
5. In order to improve the efficiency of early prevention, the availability of the medical examinations for patients with high risk should be made easier. Prevention programs or better communication could support this aim.
6. Involving dieticians in the metabolic control and diabetes care is mandatory to be able to reach the goal, the proper metabolic state.
7. Metformin therapy may reduce the development of cancer in people living with diabetes.
8. In addition to any diabetes therapy and preventive efforts for patients, the active lifestyle and the daily activity will help to improve the metabolic state and thus the decrease of insulin resistance.
9. The high incidence of oral cancer among diabetic patients strengthen the need for more regular dental visits, which is currently freely available in the local dentists or in Dental Departments of Universities or Hospitals.
10. To create a currently not existing Patient Register System, where the data of diabetic patients could be registered and available for dentists. This register could help to direct the patients into a special care department for further treatments.

### **3.4.2. Madrid consensus**

European Federation of Periodontology (EFP) and International Diabetes Federation (IDF) organized a common two-day workshop in Madrid in 2017, involved international

specialists from around the world who reviewed the scientific evidence on the relationship between diabetes and periodontitis. I was represented the IDF and was there as the only person with diabetes. A scientific consensus was obtained on the links between periodontitis and diabetes, along with guideline for dentists, physicians, and patients.

#### **4. Summary**

According to our data, over the past 15 years the incidence of oral cancer among type 2 diabetic patients has increased almost for its double, and among patients with elevated blood glucose elevated more than its double. This means that almost half of the patients we have studied suffered from metabolic disorders (IFG or DM). According to our new studies, gingiva cancers were the most common besides mouth tumors. The incidence of IFG and DM has elevated dramatically over the past 15 years among oral cancer patients, therefore the regular dental visits are well recommended for the 50 years older patients with diabetes especially for smokers. According to our experimental data, the most commonly used local anesthetics (articaine, lidocaine) inhibited the stimulation-evoked and increased the resting release of NA in the prefrontal cortex and spinal cord slices, prepared from diabetic or non-diabetic rats. These data indicate that these anesthetics inhibit the Na<sup>+</sup> and K<sup>+</sup> channels. In the comparison of non-diabetic and diabetic rats, there was no significant difference in the resting release of NA evoked by lidocaine or articaine. The augmentation of resting release evoked by articaine in the same concentration as that of lidocaine was more pronounced in the preparations from diabetic and non-diabetic rats. Articaine may have neurotoxic effects due to the huge amount of toxic, NA metabolites and due to its thiophene ring with high-solubility. The optimization of the dose of articaine in the treatment of diabetic patients with neuropathy needs consideration.

International guidelines by EFP and IDF emphasizing the importance of dental care have been formulated for diabetologists, dentists and patients. Oral inflammation, periodontitis, and other oral diseases, and the metabolic conditions affect each other. Interdisciplinary collaboration is very important in domestic and international practice with the task of the early prevention and sharing of knowledge.

## 5. Publications

1. **Végh D**, Bányai D, Ujpál M (2015) A diabetes mellitus előfordulási gyakoriságának változása malignus szájüregi daganatos betegek körében hosszútávú összehasonlító vizsgálat alapján. Fogorvosi Szemle 108, 9-12
  
2. **Végh D**, Bányai D, Hermann P, Németh Z, Ujpál M (2017) Type-2 Diabetes Mellitus and Oral Tumors in Hungary: A Long-term Comparative Epidemiological Study. ANTICANCER RESEARCH 37 (4), 1853-1857  
**Impact factor. 1,895**
  
3. **Végh D**, Somogyi A, Banyai D, Lakatos M, Balogh M, Al-Khrasani M, Furst S, Vizi ES, Hermann P (2017) Effects of articaine on [<sup>3</sup>H]noradrenaline release from cortical and spinal cord slices prepared from normal and streptozotocin-induced diabetic rats and compared to lidocaine. Brain Research Bulletin 135, 157-162.  
**Impact factor: 3.03**
  
4. Sanz M, Ceriello A, Buysschaert M, Chapple I, Demmer RT, Graziani F, Herrera D, Jepsen S, Lione L, Madianos P, Mathur M, Montanya E, Shapira L, Tonetti M, **Vegh D** (2017) Scientific evidence on the links between periodontal diseases and diabetes: Consensus report and guidelines of the joint workshop on periodontal diseases and diabetes by the International Diabetes Federation and the European Federation of Periodontology. Diabetes Res Clin Pract. 2018; 137: 231-241.  
**Impact factor: 3.639**
  
5. Sanz M, Ceriello A, Buysschaert M, Chapple I, Demmer RT, Graziani F, Herrera D, Jepsen S, Lione L, Madianos P, Mathur M, Montanya E, Shapira L, Tonetti M, **Vegh D** (2018) Scientific evidence on the links between periodontal diseases and diabetes: Consensus report and guidelines of the joint workshop on periodontal diseases and diabetes by the International Diabetes Federation and the European Federation of Periodontology. J Clin Periodontol. 2018;45(2):138-49.  
**Impact factor: 3.477**

## Acknowledgments

My sincere gratitude to associate professor Dr. Márta Ujpál for her help, without her support I could not start and get through the labyrinth of science, she had time and patience to support me.

Special thanks to Dr. Peter Hermann, Vice President of Semmelweis University who has supported me all the time and has provided the opportunity to be involved in the research with new opportunities and collaborations with others.

I appreciate and thank the help given by Prof. E. Sylvester Vizi the member of the Hungarian Academy of Sciences. He gave me the opportunity to do experimental work in his laboratory, thank for his guidance, which I accepted with great respect.

I am grateful to Dr. Gabriella Zsilla who helped me to organize my experiments and to prepare my Ph.D. thesis.

I thank Dr. Marcell Lakatos for his useful help, Gaborné Bagó, Judit Ószi and Katalin Windisch for their work. I thank associate professor Dr. Al-Khrasani Mahmoud for the diabetic animals in my animal experiments.

I thank all my teachers, mentors and colleagues, who helped me directly or indirectly during my research, inspired me and gave me faith.

I thank the support of the colleagues of the Institute of Experimental Medicine HAS, Semmelweis University Faculty of Dentistry, and the Hungarian Diabetes Association. Moreover, thank the opportunity to the IDF and EFP for the opportunity to participate in their publication.

I sincerely and gratefully thank my Parents, my Wife, and my Brother for their patience and for their long lasting support.