XEROSTOMIA AND SALIVARY LEVELS OF GLUCOSE AND UREA IN PATIENTS WITH DIABETES

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Abstract: Examination of the composition of saliva in patients with diabetes may be useful for understanding why oral manifestations occur and how they should be treated. The purpose of this study was to determine the degree of severity of xerostomia, salivary concentrations of glucose and urea in patients with insulin-dependent diabetes, and to determine the correlation between xerostomia and salivary glucose levels.

For the realization of this goal, the study included 60 patients of both sexes aged 30–70 years. The sample was divided into two groups. The first, experimental, group consisted of 30 patients who had insulin-dependent diabetes mellitus. The control group consisted of 30 subjects who were not suffering from diabetes. To determine the degree of severity of xerostomia among all respondents a questionnaire recommended by Carda was used. From all patients in both the control and experimental group, total saliva was collected for 10 minutes for biochemical analysis in accordance with the recommendations of Navazesh. Salivary glucose was determined by using the enzymatic method with a hexokinase (mmol/l), and salivary urea by using the kinetic method with urease and glutamate dehydrogenase (mmol/l). Varying degrees of xerostomia were noticed in 80% of the experimental group and only 10% of the control group. In diabetics, we found significantly higher levels of urea (2.36 mmol/l) and glucose (0.022 mmol/l) in the saliva compared with the values of these parameters (1.48 mmol/l, 0.017 mmol/l) in the control group. Based on these results, we concluded that diabetes is a disease that causes xerostomia and there is a significant correlation between the degree of xerostomia and the salivary level of glucose.

Key words: diabetes, saliva, urea, glucose.
Diabetes is a disease whose base is a metabolic disorder characterized by chronic hyperglycaemia. The occurrence of hyperglycaemia is a result of the absolute or relative lack of insulin and hepatic gluconeogenesis [6, 1]. The prevalence of the disease has shown an increasing growth in recent years. If in 2000 180 million people worldwide suffered from diabetes, in 2025 that number is expected to be 320 million [29, 32]. Diabetes is characterized by a complex clinical manifestation and a number of complications, such as: nephropathy, retinopathy, neuropathy and cardiovascular diseases [24, 3]. In patients with diabetes numerous oral complications are present, such as: xerostomia, tooth loss, gingivitis, periodontitis, odontogenic abscesses, lesions of the oral mucosa [24, 18, 15]. Iavuzilmaz [33] and Dodds [7] indicate that the disturbed secretion of saliva and its distortion of composition are the reasons for the occurrence and severity of a number of oral complications in diabetic patients. These authors also point out that an examination of the composition of saliva in patients with diabetes may be useful for understanding why oral manifestations occur and how they should be treated. Data from the literature suggest that diabetes mellitus is characterized by changes in salivary composition and function. Qualitative and quantitative changes in saliva cause violation of oral homeostasis, with oral tissues becoming sufficiently sensitive and resistant to various external threats Knox [11]. However, knowledge about the effect of diabetes on the composition of saliva and its function remains unclear.

Mangos [19] points out that in patients with diabetes the permeability of acinar cells of the parotid gland increases. This provides an increase in the ultrafiltration of blood serum components such as glucose, amylase and blood proteins. Therefore, an increase in the concentration of these components in the saliva of diabetic patients occurs [20, 9, 19]. Many studies have revealed increased levels of salivary glucose in patients with diabetes mellitus [26, 11, 8, 17].

Saliva is an organic fluid that may indicate both local and systemic disorders, with particular constituent components of saliva that may be correlated with humoral, immune, neurological, nutritional and metabolic conditions in the individuals [31]. Glucose is a small molecule that is able to pass through the endothelium of blood vessels and through the gingival sulcus and gingival fluid is secreted into the saliva. Elevated blood glucose in diabetics can cause increased salivary levels of glucose. As a consequence it can disrupt homeostasis and increase sensitivity to the occurrence of oral diseases. The literature records contradictory data from comparative analysis of blood and salivary glucose.

Some of the literature data point out that the increased serum levels of glucose in patients are linked to the increased incidence of caries occurrence [13, 27, 30], periodontal disease [30] and candidiasis [14].

Carda [5] examined the biochemical properties of saliva and the presence of xerostomia in patients with diabetes mellitus type-2. The results sho-
wed that patients with this type of diabetes have increased levels of urea in saliva and total salivary proteins, but reduced values of microglobulin in saliva. Salivary glucose was elevated only in patients with poorly controlled diabetes. Clinical symptoms of xerostomia were present in 76.4% of patients with diabetes mellitus type-2.

The aim of article

To determine the degree of severity of xerostomia, salivary concentrations of glucose and urea in patients with insulin-dependent diabetes, and to determine the correlation between xerostomia and salivary glucose levels.

Materials and Methods

For the realization of the defined objective the study included 60 patients of both sexes between the ages of 30 and 70 years. All subjects were divided into two groups.

- The first experimental group consisted of 30 subjects who had insulin-dependent diabetes mellitus. These patients were recruited from patients from the Endocrinology, Diabetes and Metabolic Disorders Clinic, at the Medical Faculty, Skopje.

The second, control, group consisted of 30 patients who did not have diabetes. These subjects were drafted at the University Dental Clinical Centre, Skopje. For inclusion in the experimental group, patients had to have insulin-dependent diabetes mellitus. The qualification for inclusion of subjects in the control group was not to have diabetes mellitus.

Testing (either in the experimental or control group) excluded individuals who smoked, alcoholics, pregnant women, individuals who had undergone surgery of the salivary glands, individuals who had been exposed to radiation of the head and neck area and individuals suffering from Sjogren's syndrome, rheumatoid arthritis or lupus erithematodes.

Special questionnaires have been developed for determining the degree of severity of xerostomia. The study used the questionnaire recommended by Carda, 2006 [5]:

**Question A:** Have you had a feeling of dryness in the mouth in the last 6 months? Yes/no.

**Question B:** How much saliva do you have in your mouth? A little / enough / a lot.

**Question C:** Do you have difficulty swallowing food? Yes/no.

**Question D:** Do you have to take liquid to facilitate swallowing food? Yes/no.
Based on the answers to these questions we determined the degree of severity of xerostomia.

**Xerostomia 1**: only when there is a positive answer to question A.

**Xerostomia 2**: when there is a positive answer to question A and one positive response (B, C or D).

**Xerostomia 3**: when there is a positive answer to question A and two other positive responses (B, C, or D).

In all patients, both in the control and the experimental group, we gathered the total saliva for chemical analyses in accordance with the recommendations of Navazesh [22] for 10 minutes. Subjects were advised one hour before the collection saliva not to eat, not to smoke, not to drink coffee, tea or cola and not to brush their teeth. The collection of saliva was performed at the same time of day (10–11h) in all subjects.

Salivary levels of glucose and urea were assessed, using a biochemical analyser INTEGRA 400 – Roche, in the biochemical laboratory of the Surgical Clinics at the Medical Faculty in Skopje, as follows:

- Salivary glucose – by the enzymatic hexokinase method (mmol/l).
- Urea in the saliva – by the kinetic method with urease and glutamate dehydrogenase (mmol/l).

The collected data were statistically analysed using the Statistic 7.0 for Windows computer programme.

**Results and discussion**

The tool that enables oral homeostasis is saliva, and all of its organic and inorganic ingredients.

Beside its other functions, saliva plays an important role in the regulation of water metabolism in the body. When, due to some certain reasons, there is a significant reduction in the amount of body water (dehydration), there is a significant reduction in saliva secretion. This "saves" water in the human body.

Through saliva secretion some substances are eliminated from the body. This is the case with end metabolites (urea, uric acid, bilirubin, etc.). But this way of elimination of metabolic end products is less important than the elimination of these metabolites via the kidneys and digestive system.

Xerostomia is a subjective feeling of dryness in the mouth, which is caused by salivary hypofunction. Xerostomia symptoms are more frequent among the elderly population, but they are not directly associated with the increasing age of the individual.
Many authors believe that xerostomia in the elderly population is associated with a higher presence of general diseases in this population and the increased use of drugs [21, 10, 33, 25, 12, 4].

In the literature there are different data on the presence of xerostomia in the elderly population, 13–60% [25, 12, 4].

During our research for establishing the degree of severity of xerostomia, we used a questionnaire recommended by Carda, 2006 [5]. Several previous studies [23, 16] indicate that the results from a questionnaire on xerostomia do not always correlate with the actual flow of saliva in the mouth.

In fact, the authors found that 34% of patients who had hyposalivation did not complain of subjective symptoms of xerostomia, whereas in 37% of patients with xerostomia reduced saliva production was not determined.

We believe that the questionnaire we used to determine the degree of xerostomia is a good model for screening hyposalivation in patients with diabetes.

The results obtained in our study showed that in 24 (80%) patients with diabetes xerostomia was present, whereas only 3 (10%) subjects in the control group registered a subjective feeling of dryness in the mouth.

In the group of patients with diabetes, in whom we evaluated xerostomia, 10 (33.3%) patients had a first degree of xerostomia, 6 (20%) of them had a second degree, and 8 (26.7%) had a third degree of xerostomia (Table 1).

<table>
<thead>
<tr>
<th>Xerostomia level/group</th>
<th>Examined</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>number</td>
<td>%</td>
</tr>
<tr>
<td>0</td>
<td>6</td>
<td>20.0</td>
</tr>
<tr>
<td>1</td>
<td>10</td>
<td>33.3</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>20.0</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>26.7</td>
</tr>
</tbody>
</table>

We believe that the Xerostomia which we registered in our patients with diabetes results from the negative effects of diabetes on the sympathetic and parasympathetic nervous systems, which play a key role in the secretion of saliva. Also, far greater dehydration of the organism of diabetics and hormonal changes are factors which cause decreased saliva production in these patients.
Urea is a diamide of carbonic acid. Salivary glands do not synthesize urea, but it reaches them through the ultra filtration of blood serum, on the level of acinar cells in the salivary glands.

Urea as an end product of protein catabolism in solutions behaves as a moderately alkaline compound. This compound is of low molecular weight and can easily pass through the membrane of the acinar cell through ultra filtration.

The average value of urea in the saliva of our patients in the control group was 3.83 mmol/l. The mean value of urea in the saliva of patients with diabetes was 8.19 mmol/l (Table 2).

Table 2

<table>
<thead>
<tr>
<th>Group/urea mmol/l</th>
<th>Number</th>
<th>Average</th>
<th>Minimum</th>
<th>Maximum</th>
<th>± Dev.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>30</td>
<td>3.83</td>
<td>1.48</td>
<td>9.69</td>
<td>2.104494</td>
</tr>
<tr>
<td>Examined</td>
<td>30</td>
<td>8.19</td>
<td>2.36</td>
<td>26.84</td>
<td>4.260465</td>
</tr>
</tbody>
</table>

According to the Mann-Whitney U test differences between the average values of urea in the saliva of patients between the two groups is statistically significant at p = 0.000000 (Table 3). Elevated values of salivary urea in patients with diabetes were noted by Carda [5] in his researches.

Table 3

<table>
<thead>
<tr>
<th>Rank Sum Group 1</th>
<th>Rank Sum Group 2</th>
<th>U</th>
<th>Z</th>
<th>p-level</th>
</tr>
</thead>
<tbody>
<tr>
<td>570.0000</td>
<td>1260.000</td>
<td>105.0000</td>
<td>-5.10063</td>
<td>0.000000</td>
</tr>
</tbody>
</table>

In our study serum urea concentrations have not been studied. But considering the nature of diabetes as a metabolic disease that causes disruption of metabolic processes in the human body, it is likely that serum levels of urea in patients with diabetes are elevated. Elevated levels of serum urea in patients with diabetes may be due to dietary regime and increased intake of protein in the diet of these patients. The increased permeability of acinar cells in the parotid gland in patients with diabetes allows enhanced ultra filtration of blood.
serum components and even of urea. We believe that the significantly higher values of salivary urea in patients with diabetes are based on these processes.

In this study, we registered significantly higher levels of salivary glucose in patients with diabetes compared with the level of glucose in the control group of respondents (Tables 4 and 5). Also, the Spearman correlation coefficient registered a statistically significant correlation (= 0.422528, p < 0.05) between the degree of xerostomia and salivary glucose levels in patients in the experimental group. These results are consistent with the findings of Aydin [2], Ben-Aryeh [4] and Carda [5].

Table 4

<table>
<thead>
<tr>
<th>Group</th>
<th>Number</th>
<th>Average</th>
<th>Minimum</th>
<th>Maximum</th>
<th>± Dev.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>30</td>
<td>0.017</td>
<td>0.0</td>
<td>0.13</td>
<td>0.036498</td>
</tr>
<tr>
<td>Examined</td>
<td>30</td>
<td>0.022</td>
<td>0.0</td>
<td>0.35</td>
<td>0.063049</td>
</tr>
</tbody>
</table>

Table 5

<table>
<thead>
<tr>
<th>Rank Sum Group 1</th>
<th>Rank Sum Group 2</th>
<th>U</th>
<th>Z</th>
<th>p-level</th>
</tr>
</thead>
<tbody>
<tr>
<td>790.0000</td>
<td>1040.000</td>
<td>325.0000</td>
<td>-2.02819</td>
<td>0.042542</td>
</tr>
</tbody>
</table>

Karjalainen [14] and Reuterving [28] indicate that salivary glucose levels rise only when the level of serum glucose increases. Glucose as a small molecule diffuses easily through semi-permeable membranes, because of which when levels of serum glucose are increased, they can easily reach the salivary secretion by ultrafiltration. The impaired permeability that is present in diabetic patients occurs as a result of changes in the basement membrane and may be an additional reason for the increase in salivary glucose. However, the increased level of glucose in the saliva favours proliferation and colonization of microorganisms in the oral cavity. Glucose serves as a base for the development of Candida albicans, and also inactivates the activity of neutrophils. Oral diseases that may be associated with increased glucose levels in saliva are: candidiasis, dental caries, gingivitis and periodontal disease, increased risk of infection, stomatodynia and difficult healing of wounds.
Conclusions

1. In patients with diabetes, salivary concentrations of urea and glucose were significantly increased.
2. Diabetes is a disease that causes xerostomia.
3. A significant correlation between the degree of xerostomia and the salivary level of glucose was registered.

References


Резиме

КСЕРОСТОМИЈА И САЛИВАРНИ НИВОА НА ГЛУКОЗА И УРЕА КАЈ ПАЦИОНТИ СО ДИЈАБЕТ

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Апстракт: Испитувањето на составот на плунката кај пациентите со дијабет може да биде од полза за разбирање, зошто се јавуваат оралните манифестации и како истите да се третираат. Целта на овој труд е да се утврди степенот на изразеност на ксеростомија, саливарните концентрации на глукоза и уреа кај пациенти со инсулин зависен дијабет, и да се утврди корелацијата помеѓу сувоста на устата и саливарните нивоа на гликоза.

За реализацијата на целта во испитувањето беа вклучени 60 испитаници од двата пола на возраст од 30–70 години. Примерокот на испитаници го поделимме на две групи. Првата група, експерименталната, ја сочинуваа 30 испитаници кои имаа инсулин зависен Diabetes Mellitus. Втората група, контролната, ја сочинува 30 испитаници кои не се заболнени од дијабет. За одредување на степенот на изразеност на ксеростомијата кај сите испитаници го користевме прабалникот препорачан од Carda. Каж сите испитаници, и од контролната и од испитуваната група колекционираевме вкупна плунка за биохемиска анализа според препораките на Navazesh во траење од 10 минути. Саливарната глукоза ја одредувааме со помош на ензиматска метода со хексокиназа (mmol/l), додека пак уреата во плунка со помош на кинетичка метода со уреаза и глутамат дехидрогеназа (mmol/l).
Кај 80% од испитуваната група и само кај 10% од kontrolната група регистрирање различен степен на ксеростомија. Кај дијабетичарите утврдивме синцификаантно повисоки вредности на уреа (2,36 mmol/l) и глукоза (0,022 mmol/l) во плунка во споредба со вредностите на овие параметри (1,48 mmol/l, 0,017 mmol/l) кај контролната група.

Врз основа на добиените резултати заклучивме дека дијабетот е заболување кое предизвикува ксеростомија и постои значителна корелација помеѓу степенот на ксеростомија и саливарното ниво на глукоза.

Ключни зборови: дијабет, плунка, уреа, глукоза.

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