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The Impact of Antihypertensive Medications on Quantitative and Qualitative Characteristics of Saliva.

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ABSTRACT

To determine the quantitative and qualitative characteristics of the saliva of patients treated with antihypertensive medications. 60 subjects, aged 30-70 were included whereby an experimental group involved 30 patients at antihypertensive drugs. In control group (30) subjects didn't receive any medications. Unstimulated saliva was collected of all participants according Navazesh recommendations. A biochemical analyzer INTEGRA 400- Roche was used to determine total salivary proteins, urea, albumin, calcium, sodium and potassium levels in saliva. Computer programs Statistica 7.1 and SPSS 17 were used. The amount of unstimulated saliva was significantly decreased in experimental group. Increased saliva amounts of K^+, Na^+ and urea were noted in this group. The total proteins were insignificantly increased, while the amounts of Ca^{2+} and albumin did not differ significantly between the two groups. Antihypertensive medications significantly influence the salivary composition which can cause disruption of the oral homeostasis.

Keywords: antihypertensive medications, saliva, saliva components, electrolytes

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INTRODUCTION

Oral fluid (whole saliva) is for the larger part produced and secreted by the three major paired salivary glands, such as the parotid, submandibular and sublingual, and numerous minor glands located throughout the oral cavity. Saliva has several types of functions that are of profound importance for the oral health. It plays the most important role in the oral homeostasis. Absence of saliva in the oral area is a precondition for a number of oral diseases; not only teeth will rapidly decay, but also the oral mucosa will become vulnerable to bacterial, viral and fungal infections.

The unstimulated, mixed saliva is a product of the total gland apparatus in the oral cavity, when there are no any substances to stimulate the gustative and other receptors. Stimulated saliva is a result of the influence of different factors in the oral cavity, under stimulation of a number of receptors in the mouth. The amount of stimulated saliva is significantly higher (1.5-2.0 ml/min) than the unstimulated. The saliva secretion is regulated by the central nervous as well as the endocrine system. The central nervous system has a main role in the saliva regulation. There are 3 centers which regulate the function of the salivary glands and the salivation:

- Primary center salivation, localized in the medulla oblongata,
- Secondary center salivation, localized in the thalamus (brain intersection of the sensitive nerves)
- Tertiary center salivation, localized in the opercula- insular zone of the cerebral cortex.

The endocrine system has the main role in saliva secretion, especially, the cortex of the adrenal glands, which secretes many hormones in the blood. The most important for the salivation is mineral-corticoid hormone- aldosterone. In the salivary glands, on the collection tubules, aldosterone participates in the regulation of the metabolism of sodium and potassium, and indirectly participates in the regulation of the metabolism of chlorine. Under the influence of aldosterone, Na^+ is reabsorbed from the salivary glands in the blood, while the K^+ is secreted in definite saliva. Thanks to this role of aldosterone, saliva is a body fluid richest in potassium [1].

The saliva secretion is also greatly influenced by catecholamines, adrenalin, hormone of medulla of the adrenal glands and the sympathicus nervous endings. Binding with the α-receptors of the endothelial cells from the blood vessels, including the blood vessels of the salivary glands, they cause their vasoconstriction. This decreases the salivary flow. In case of psychological stress, which is accompanied with increased adrenaline secretion, only a small amounts of thick, sticky (mucosa) saliva is secreted (i.e sympathicus saliva) [2].

The decrease level of saliva secretion is noted as a side effect of more than 500 medications [3] which belongs to 42 pharmacological groups [4]. Groups of drugs that commonly cause decreased saliva secretion are: diuretics, antihypertensive drugs, ACE- inhibitors, medications for treating diabetes etc. A large number of drugs, used for treating heart diseases, also belong to the group that causes decreased level of saliva secretion [5]. According to many authors [6-10] that's the reason for the presence of symptoms of dry mouth (20 - 46%) at patients over 65 years.

The aim of this paper is to determine the influence of the antihypertensive medications on the quantitative and qualitative features of saliva.

MATERIAL AND METHOD

To achieve the set aim, a total of 60 patients, both sexes, male and female, aged 30-70 were included in the study. All participants were divided in two groups. The first one, the experimental group, consisted of 30 subjects who are receiving antihypertensive therapy (AHT). The second one- control group, consisted of 30 participants who did not receive any medications. In the study were not include individuals who smoked, alcoholics, pregnant women, individuals with surgical intervention of the salivary glands, patients who received radio therapy in the area of the head and the neck, as well as individuals suffering from the Sjögren syndrome, rheumatoid arthritis and Lupus erythematodes.

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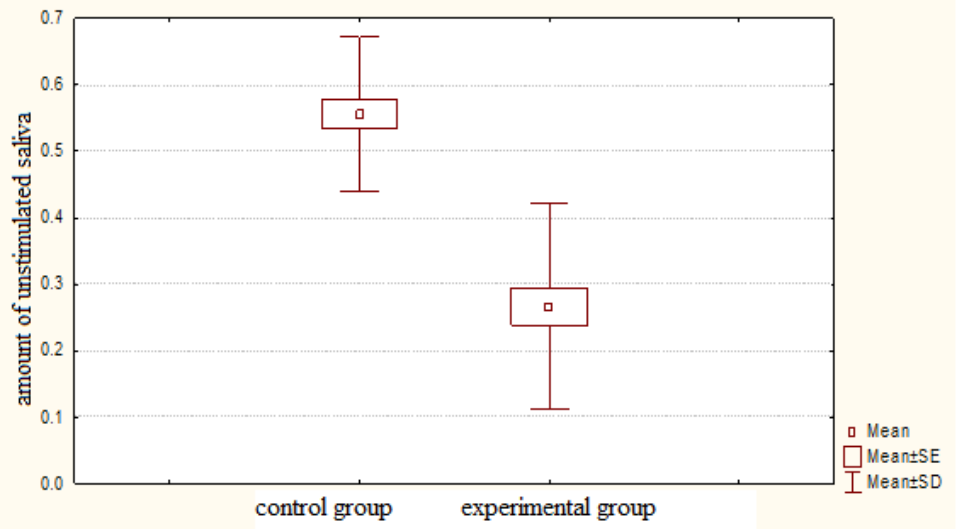
A total unstimulated saliva was collected from all of the participants, in accordance with the recommendations from Navazesh [11] in duration of 10 minutes. The biochemical parameters of the saliva were analyzed with the biochemical analyzer INTEGRA 400 – Roche in the biochemical laboratory of the Surgical clinics at the Faculty of Medicine in Skopje. It involved: urea in saliva – kinetical method with urease and glutamate dehydrogenases (mmol/L); Total salivary proteins – Biuret reaction (g/L); Albumin modified bromine cresol test (g/L); Calcium- Schwarzenbach method with o-cresolphthalein complex (mmol/L); sodium and potassium – ion selective electrode method with automatic dilution (mmol/L). The collected data were statistically processed by specific computer programs Statistica 7.1 for Windows and SPSS 17.

RESULTS AND DISCUSSION

Human saliva is a complex biological fluid, which contains a large number of inorganic (e,g. Ca^{2+}, K^{+}, $Na^{+,}$ phosphate and bicarbonate) and organic (glyco) proteins and peptides) constituents with important functions for the maintenance of oral health. Saliva protects the oral tissues in various ways. Upon stimulation, the cleansing action of the continuous flow of watery saliva clears the mouth from bacteria and food particles. Buffering ions, particularly bicarbonate, aid in acid neutralization, in this way protecting dental enamel against demineralization. Thus, patients with chronic dry mouth are prone to develop caries, because of the diminished protection by saliva, are highly susceptible for development of oral infections [12].

The amount of unstimulated saliva under physiological conditions is 0.4 – 0.5 mL/min. But, this data is difficult to take for definite, because the values of saliva secreted shows a number of individual variations. The amount of secreted saliva from 0.2-0.4 mL/min indicates presence of oligosialia, while the amount of saliva less than 0.2 mL/min points to xerostomia.

Graph 1: Graphical representation of the average values of the amount of unstimulated saliva for both groups



The average amount of unstimulated saliva in the control group subjects is as follows: 0.6 ± 0.1, min. 0.3, and max 0.8. The average amount of unstimulated saliva at the patients of the experimental group is 0.3 ± 0.2, min. 0.1, max. 0.6. The results of our research show that the average values of unstimulated saliva at AHT patients were *x* =0.3 mL/min, while at the control group were *x* = 0.6 mL/min (graph 1). The difference between the average values of unstimulated saliva in the two groups of participants was statistically significant for p=0.000000 (tab. 1).

Table 1: Representation of Mann-Whitney U test

Rank Sum Group 1	Rank Sum Group 2	U	Z	p-level
1276.500	553.5000	88.50000	5.344570	0.000000

According to the Mann-Whitney U test, the difference between the average values of the unstimulated saliva at the participants from both groups is statistically significant for p=0.000000 (table 1).

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Our results comply with Nederfors et al. [13] and Rafi et al. [14]. A large number of literature data suggests that there are significant differences of the AHT effect on saliva secretion. But, most of them point that the patients with AHT, show lower level of saliva secretion.

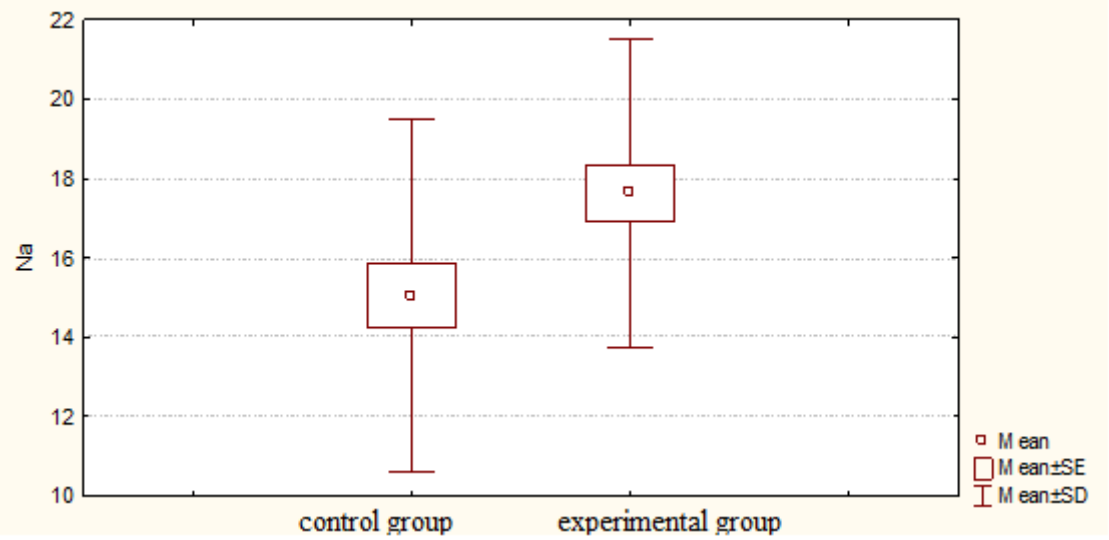
The group of antihypertensive medications involves a number of medications such as: diuretics, heart glycosides, antihypertensive drugs with central effect, α-adrenergic blockaders, β-adrenergic blockaders, angiotensin-converting enzyme inhibitor (ACE inhibitors), calcium channel blockers etc.

They all have different mechanisms of action. Some of them act selectively, affect the kidneys and the heart, while others are called non-selective antihypertensive medications.

The patients we followed in our study were recruited at the clinic of Cardiology at the Medical Clinic Center in Skopje. They could not be grouped according to the type of the medication they take to regulate their blood pressure, because most of them were taking a combination of two or more antihypertensive drugs. The lower salivary flow at the patients with AHT is directly connected with the increased diuresis at patients who take diuretics in treatment of blood pressure. The increased diuresis causes reduction of the total extracellular liquid which directly influence the salivary production. However, the drugs belonging to the group of calcium- blockers, can also cause lower salivary secretion. Namely, inositol-3-phosphate and Ca, have a significant role in the regulation of the secretion of water and electrolytes by the salivary glands.

The concentration and the ratio between the electrolytes in the saliva can significantly vary depending of the intensity of the stimulation and the amount of saliva secretion.

Graph 2: Graphical representation of the average values of Na^+ in the saliva at the patients from both groups



The average values of Na+ in the saliva of the control group subjects are 15.05 ±4.4mmol/L, min. 3.17mmol/L, and max. 20.0 mmol/L. The average values of Na+ in the saliva at the patients of the experimental group are 17.6 ±3.8mmol/L, min. 8.9mmol/L, max. 28.9 mmol/L.

Table 2: Representation of Mann-Whitney U test

Rank Sum Group 1	Rank Sum Group 2	U	Z	p-level
776.5000	1053.500	311.5000	-2.04764	0.040596

According to the Mann-Whitney U test the difference between the average values of Na+ in the saliva of the subjects from both groups is statistically significant for p=0.040596 .

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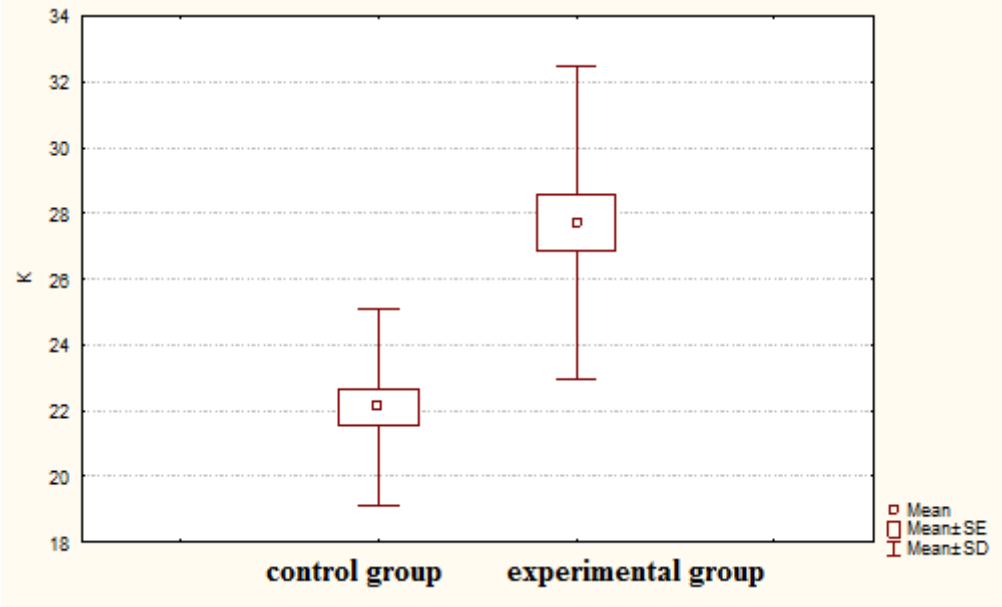
Graph 3: Graphical representation of the average amount of K+ in the saliva of the patients from both groups



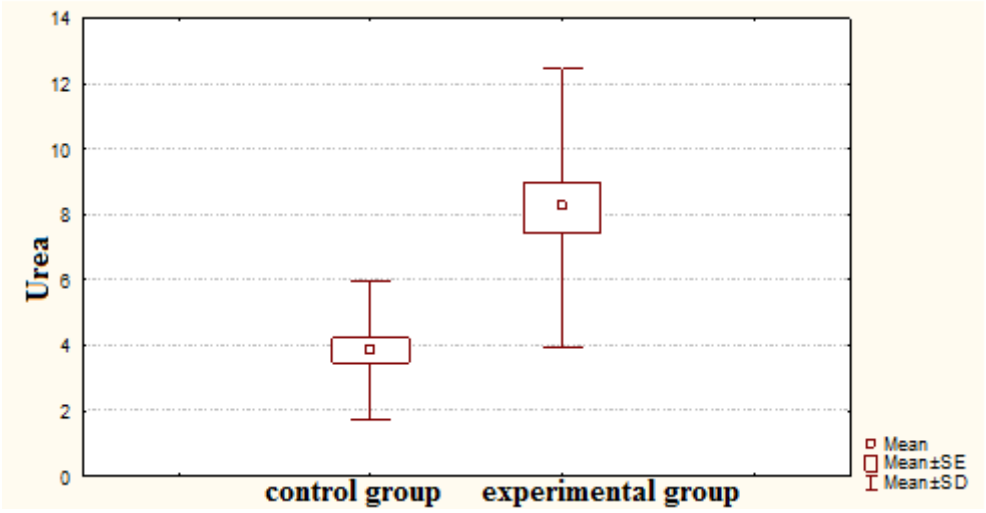
The average values of K+ in the saliva of the participants in the control group are 22.11 ± 3.0 mmol/L, min. 13.86 mmol/L, and max. 27.51 mmol/L. The average values of K+ in the saliva at patients of the experimental group are 27.71 ± 4.8 mmol/L, min. 17.74 mmol/L, and max. 44.52 mmol/L.

Table 3: Representation of Mann-Whitney U test

Rank Sum Group 1	Rank Sum Group 2	U	Z	p-level
566.0000	1264.000	101.0000	-5.15976	0.000000

According to Mann-Whitney U test the difference between the average values of K+ in the saliva of the respondents from both groups is statistically significant for p=0.000000.

Graph 4: Graphical representation of the average values of urea in the saliva of the respondents from both groups



The average values of urea in the saliva of the subjects from the control group are 3.83 ±2.1mmol/L, min.1.48mmol/L, max. 9.69 mmol/L. The mean values of urea in the saliva from the patients of the experimental group are 8.19 ±4.3mmol/L, min. 2.36 mmol/L, max. 26.84 mmol/L.

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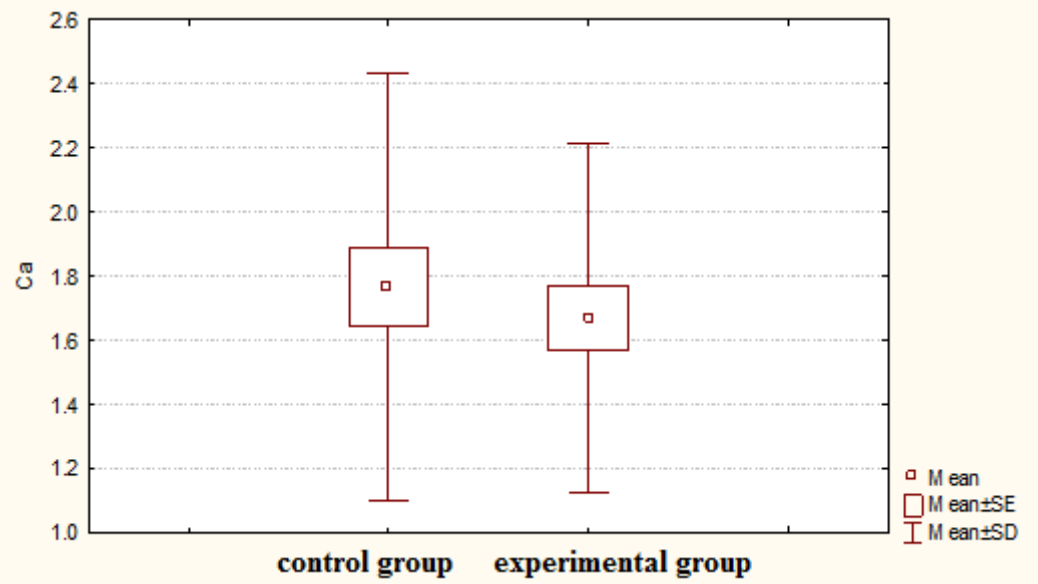
Table 4: Representation of the Mann-Whitney Utest

Rank Sum Group 1	Rank Sum Group 2	U	Z	p-level
570.0000	1260.000	105.0000	-5.10063	0.000000

According to the Mann-Whitney U test the difference between the average values of urea in the saliva of the participants from both groups is statistically significant for p=0.000000.

The results of our research, showed statistically significant higher values of sodium Na^+ (graph and table 2), potassium K^+ (graph and table 3) and urea (graph and table 4) at the AHT patients, compared to the values of the salivary electrolytes at the patients from the control group.

Graph 5: Graphical representaion of the average values of Ca^{2+} in the saliva of the subjects from both groups



The average values of Ca^{2+} in the saliva at the subjects from the control group are 1.76 ± 0.67 mmol/L, min. 1.05 mmol/L, max. 4.26 mmol/L. The average values of Ca^{2+} in the saliva at the patients from the experimental group are 1.66 ± 0.54 mmol/L, min. 1.05 mmol/L, and max. 2.77 mmol/L.

Table 5: Represnetation of the Mann-Whitney Utest

Rank Sum Group 1	Rank Sum Group 2	U	Z	p-level
947.0000	883.0000	418.0000	0.473102	0.636141

According to the Mann-Whitney U test the difference between the mean values of Ca^{2+} in the saliva at the respondents from both groups is statistically insignificant for p>0.05.

The differences of the mean values of Ca^{2+} in the saliva between two groups is statistically insignificant for p>0.05 (graph and table 5).

The increased salivary concentrations of Na^+ are a result of the use of diuretics that inhibit the reuptake of Na+ on the level of the collection and drainage ducts of the salivary glands, and because of that, this electrolyte is secreted in higher concentration. If we take the fact, that a great number of diuretics do not spare the potassium, but cause its increased secretion, our result of increased salivary concentrations of potassium is logical. Similar results were noted by Rafi et al. [14] in his study, who in addition to xerostomia at patients who receive antihypertensive therapy, observed increased values of sodium and total proteins. The author believes that elevated values of potassium due to the action of blockers on the alpha- receptors.

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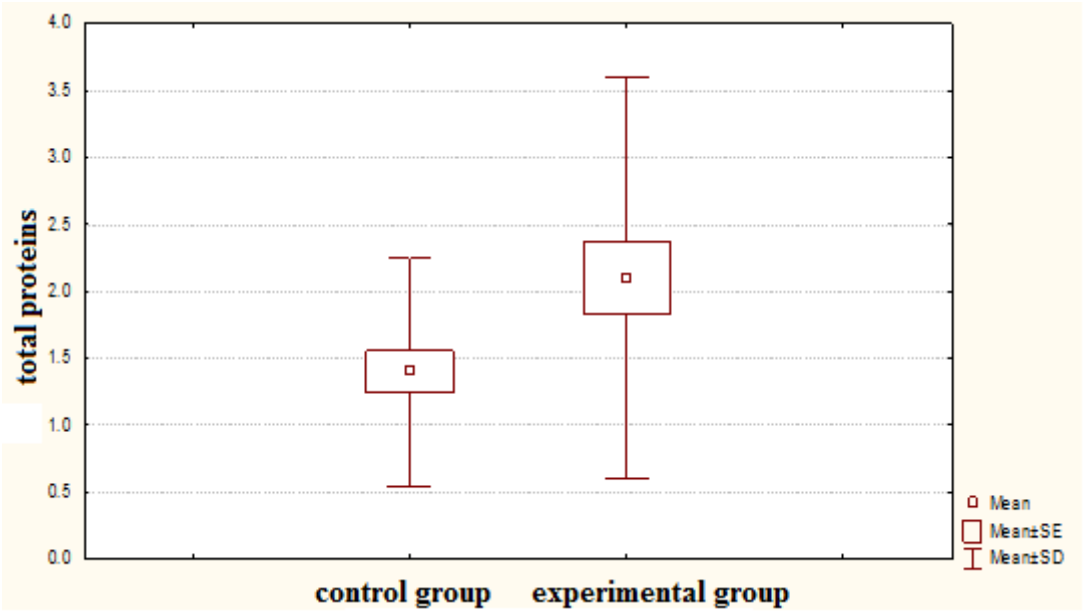
Urea is a diamide of the carbonic acid. The salivary glands do not synthesize the urea, but it arrives through ultra-filtration from the blood serum. The urea, as a final product of the protein catabolism, acts as a moderate alkaline compound. It has a small molecular mass and easily passes through the membrane of the acinus cells. The increased salivary values of urea at the patients with antihypertensive therapy can be result of the dietetic regime and the increased intake of protein in the diet of these patients.

It is interesting to note that our results of the salivary electrolytes at the patients with AHT, not comply with the results obtained by Nederfords [15 -17] in their research made in the 90´s of the past century. However, the results received the same author [18] in 2004, coincide with our findings.

The concentration of total proteins in the saliva at the patients with antihypertensive therapy is higher than in the control subjects.

Graph 6: Graphical representation of the average values of total proteins in the saliva at the subjects from both groups



The average values of the total proteins in the saliva at the participants from the control group are 1.4 ± 0.85 g/L, min. 0.0 g/L, max. 4.0 g/L. The average values of total proteins in the saliva at the subjects from experimental group are 2.1 ± 1.5 g/L, min. 1.0 g/L, max. 7.0 g/L.

Table 6: Representation of the Mann-Whitney Utest

Rank Sum Group 1	Rank Sum Group 2	U	Z	p-level
794.0000	1036.000	329.0000	-1.78892	0.073629

According to the Mann-Whitney U test, the difference between the average values of the total proteins in the saliva from both groups is statistically insignificant for p>0.05.
But, this difference is statistically insignificant (graph and table 6). The difference between the levels of the albumin between the experimental and the control group is also statistically insignificant (graph 7 and table7).

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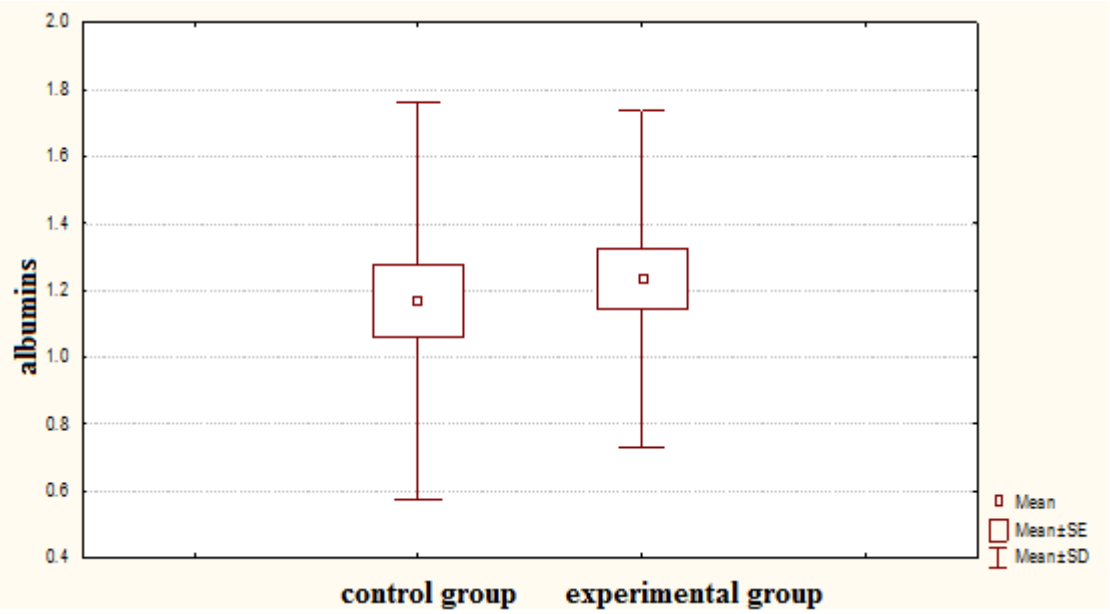
Graph 7: Graphical representation of the albumins in the saliva at the subjects from both groups



The mean value of the albumins in the saliva of the subjects from the control group is 1.2 ± 0.6 g/L, min 0.0 g/L, max. 3.0 g/L. The average values of albumins in the saliva of the experimental group are 1.2 ± 0.5 g/L, min. 0.0 g/L, and max. 2.0.

Table 7: Representation of the Mann-Whitney U-test

Rank Sum Group 1	Rank Sum Group 2	U	Z	p-level
879.0000	951.0000	414.0000	-0.532239	0.594561

According to the Mann-Whitney U test the differences between the average values of albumins in the saliva from both groups participants is statistically insignificant for p>0.05.

We suppose that, increased values of total salivary protein due to the long-term adrenergic stimulation in patients with hypertension. Significantly reduced quantity of saliva secretion and impaired concentration of electrolytes in saliva at patients with antihypertensive therapy, are risk factors of numerous oral diseases and problems, such as, increased frequency of caries, periodontal diseases, bacterial and fungal infections exc. Reduced salivary flow, caused by antihypertensive drugs is reversible process, because the salivary gland parenchyma is still preserved. Therefore, at patients with AHT, is recommended saliva secretion stimulation, primarily a local, non-systemic treatment of this type of oligosialia.

Finally, we can say that the use of saliva is attractive to monitor parameters of health and disease not only because of its multiple contributors, but also since it is noninvasive, easy to obtain, painless and there is no need to employ specially trained personnel for sample collection. The possibility to identify and measure biomarkers in saliva opens the avenue for diagnosis, early detection, monitoring progression of disease, and compliance to treatment modalities.

CONCLUSION

The antihypertensive medications significantly reduced salivary secretion as well as the salivary composition, which can cause disruption of the oral homeostasis and the appearance of a number of oral diseases such as: caries, periodontal diseases, as well as bacterial and fungal infections. Analysis of the chemical composition of saliva and electrolyte status allows us to follow the impact of AH drugs in patients with hypertension, and if we note changes in the chemical composition of saliva, to replace the appropriate drug with another.

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