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SALIVARY MARKERS IN PATIENTS WITH CHRONIC KIDNEY DISEASE

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ABSTRACT

Aim of the study: To determine the possibility of using saliva as a diagnostic and prognostic tool for screening and monitoring kidney function.

Methods: This study included 32 patients with different stages of chronic kidney disease (CKD) and 20 healthy examinees for the control group. Saliva was collected using the spitting method, and on the same day blood was also drawn from the examinees to determine serum concentrations of urea and creatinine. The salivary values of uric acid, urea, creatinine and albumin were determined with a spectrophotometer, as well as the serum concentrations of urea and creatinine.

Results: Our results showed a statistically significant positive correlation between salivary and serum levels of urea and creatinine in patients with CKD (Pearson's correlation coefficient for urea was $r = 0.6527$, $p = 0.000$, while for creatinine it was $r = 0.5486$, $p = 0.001$). We detected a statistically significant positive correlation between the salivary levels of urea and the clinical stage of CKD ($r = 0.4667$, $p = 0.007$). We did not register a significant correlation between the salivary levels of creatinine and the clinical stage of CKD ($r = 0.1643$, $p = 0.369$).

Conclusion : Salivary urea is a valid marker for determining kidney function and a potential salivary marker for screening and monitoring kidney function. Salivary creatinine can be used as a qualitative marker, only indicating the existence of a disease.

Keywords: saliva, urea, creatinine, kidney failure, chronic

INTRODUCTION

Chronic kidney disease (CKD) is a state of progressive loss of kidney function, ultimately resulting in the need for renal replacement therapy (dialysis or transplantation). Kidney damage refers to pathologic abnormalities either suggested by imaging studies or renal biopsy, abnormalities in urinary sediment, or increased urinary albumin excretion rates [1]. Even though the causes of CKD vary globally, the most common primary diseases causing CKD are diabetes and hypertension [2]. Although in a smaller percentage, other diseases such as infection, primary and secondary glomerulonephritis, chronic tubulointerstitial nephritis, cystic diseases, plasma cell dyscrasias or neoplasms can lead to the occurrence of CKD [2,3]. Genetic risk factors may also contribute to CKD risk [4].

Regardless of the nature of the pathological cause, the end result is the same – there is a gradual, significant and progressive destruction of the anatomo-functional quantum of the kidney tissue. With the reduction of the kidney tissue itself, there is a decrease in glomerular filtration, and then to a gradual disruption of the tubular and interstitial functions of the kidney, until the very end, when hormonal disorders also occur.

The result of all this is the retention of catabolites (degradation products) [5] that are created through the numerous metabolic processes in the human body. These are eliminated through renal excretion during a healthy kidney function. These catabolites include urea, uric acid and creatinine [6,7,8]. These degradation products of the metabolic processes in the human body, by way of ultrafiltration from the blood, arrive and can be detected in the saliva [9, 10, 11].

Optimal detection and subsequent risk stratification of people with chronic kidney disease (CKD) requires simultaneous consideration of both kidney function (glomerular filtration rate [GFR]) and kidney damage (as indicated by albuminuria or proteinuria) [12]. The serum level of creatinine (primarily secreted by the kidneys) is also used to determine renal function [13]. Collection of blood for serum analysis is an invasive procedure associated with fear and anxiety. Frequent blood sampling results in severe anemia and an increase in the risk of infection [5]. Therefore, a simple noninvasive diagnostic test with minimal risk that can accurately evaluate disease status would be of tremendous value to patients and clinicians. For that purpose, saliva analysis can be used, since saliva collection is a simple, non-invasive and safe method [14].

Given that saliva is increasingly used as a diagnostic material for research on this topic [15–20], and the data from the literature emphasize the need for additional scientific evidence to confirm salivary diagnostic values, the objective of this study was to determine the possibility of using saliva as a diagnostic and prognostic tool for screening and monitoring kidney function.

MATERIALS AND METHODS

This study was carried out at the Department of Oral and Periodontal Diseases at the Ss. Cyril and Methodius University in Skopje (Faculty of Dentistry – Skopje) and the PHI University Clinic of Nephrology in Skopje, and the study is in accordance with the Helsinki Declaration of 1975, as revised in 1983 and approved by the Ethics Committee of the Ss. Cyril and Methodius University in Skopje, Faculty of Dentistry - Skopje.

This study included 32 patients with different stages of CKD from PHI University Clinic of Nephrology in Skopje, as well as 20 healthy examinees for the control group. Staging of CKD based on the glomerular filtration rate (GFR) goes as follows: stage 1 (GFR ≥90 mL/min/1.73 m2), stage 2 (GFR 60–89 mL/min/1.73 m2), stage 3a (45–59 mL/min/1.73 m2), stage 3b (30–44 mL/min/1.73 m2), stage 4 (15–29 mL/min/1.73 m2), and stage 5 (<15 mL/min/1.73 m2 – kidney failure) [21].

The collection of the saliva was carried out in the Biochemical and Microbiological laboratory of the Department of Oral and Periodontal Diseases at the Ss. Cyril and Methodius University in Skopje, Faculty of Dentistry – Skopje. In some patients, saliva was collected in the hospital rooms of the PHI University Clinic of Nephrology in Skopje. All patients and examinees signed a written consent for inclusion in the study. Standard BioSystems reagents (BioSystems S.A., Costa Brava 30 08030 Barcelona, Spain) were used in the study. All the reagents used in the study were of analytical grade.

In this study, the unstimulated saliva we analyzed was collected using the spitting method, according to the directions provided by Navazesh [22]. We collected the saliva in a graduated test tube which was placed in a glass container with ice. A funnel was placed on the tube to facilitate the collection of saliva. The further processing of the saliva was carried out in the Biochemical and Microbiological laboratory of the Department of Oral and Periodontal Diseases at the Ss. Cyril and Methodius University in Skopje, Faculty of Dentistry – Skopje, and consisted of mechanically stirring up the viscous saliva using a micropipette; saliva vortexing for 2 minutes, using a Dragon LAB MX_S (Adjustable Speed Vortex) vortex device (DLAB, 1 Yu An Road, Beijing Airport Economic Core Zone, Shunyi District, Beijing 101318, China); and centrifuging the graduated plastic tubes with saliva in a Megafuge 1.0 – Heraeus centrifuge (Heraeus, Hanau, Germany) with a speed of 4000 Rcf revolutions for 10 minutes.

After processing the saliva, we took a sample of the supernatant (obtained by centrifuging the saliva) with a micropipette and transferred it into small plastic conical tubes (1.5 ml) for

freezing. The samples were frozen at -20 ºC. On the same day when saliva was collected from the participants, blood was also drawn from them at the PHI University Clinic of Nephrology in Skopje to determine serum concentrations of urea and creatinine.

After thawing the samples of saliva, the values of the following parameters were determined using the appropriate methods: uric acid (URICASE/PEROXIDASE)[23], urea (UREA/BUN-UV)[24], creatinine (JAFFE) [25], albumin (BROMOCRESOL GREEN)[26]. The examinations were carried out in the Biochemical and Microbiological Laboratory of the Department of Oral and Periodontal Diseases at the Ss. Cyril and Methodius University in Skopje, Faculty of Dentistry – Skopje with the spectrophotometer - ULTRASPEC 1000. The serum concentrations of urea and creatinine were determined using the same methods (urea – UREA/BUN-UV and creatinine – JAFFE)[24, 25] in the Laboratory for Clinical Biochemistry.

Statistical analysis was performed by Statistica for Windows 7.0 and SPSS Version 20. Student's t-test was used to determine the significance of the differences between the salivary markers in the studied and control groups. Pearson's correlation coefficient was used to determine the correlation between salivary and serum concentrations of urea and creatinine, as well as to determine the correlation between the clinical stage of CKD and salivary urea/creatinine values. The p-value <0.05 was considered statistically significant.

RESULTS

This study included 52 participants, of which 32 were patients with CKD and 20 participants were healthy individuals, included in the control group. In the examined group, 18 (56.25%) were male and 14 (43.75%) were female participants, while in the control group 11 (55.0%) were male and 9 (45.0%) were female participants.

The average age of the patients in the examined group was 54.84 ± 17.69 years, minimum 16 years, and maximum 82 years. The average age of the participants from the control group was 44.8 ± 12.61 years, minimum 24 years, and maximum 68 years.

Table 1 shows the percentage representation of patients according to the clinical stage of CKD. More than 1/3 of the patients included in this study were in the terminal stage of CKD (kidney failure).

Table 1. *Division of patients by stage of CKD*

Stage of CKD	Number of patients	%
2	4	12.50000
3	8	25.00000
4	9	28.12500
5	11	34.37500

Our results showed that the mean values of salivary urea, creatinine, uric acid and salivary albumin in patients with CKD were statistically significantly higher, compared to the values of these salivary parameters in healthy subjects (Table 2).

Table 2. *Salivary parameters in the examined and control group*

T-test for Independent Samples (CKD stat) Note: Variables were treated as independent samples					
Salivary parameters	EG*	CG**	t-value	df	p<
Urea mmol/L	11.00	3.85	5.48	50	0.000001
Creatinine µmol/L	45.06063	12.16000	5.030355	50	0.000007
Uric acid µmol/L	295.7500	146.9500	6.287824	50	0.000000
Albumin g/L	0.417500	0.242000	2.619470	50	0.011629

*Examined group, **Control group

The significantly lower salivary flow rate in the patients with CKD, compared to the salivary flow rate in the participants from the control group, is presented in Table 3.

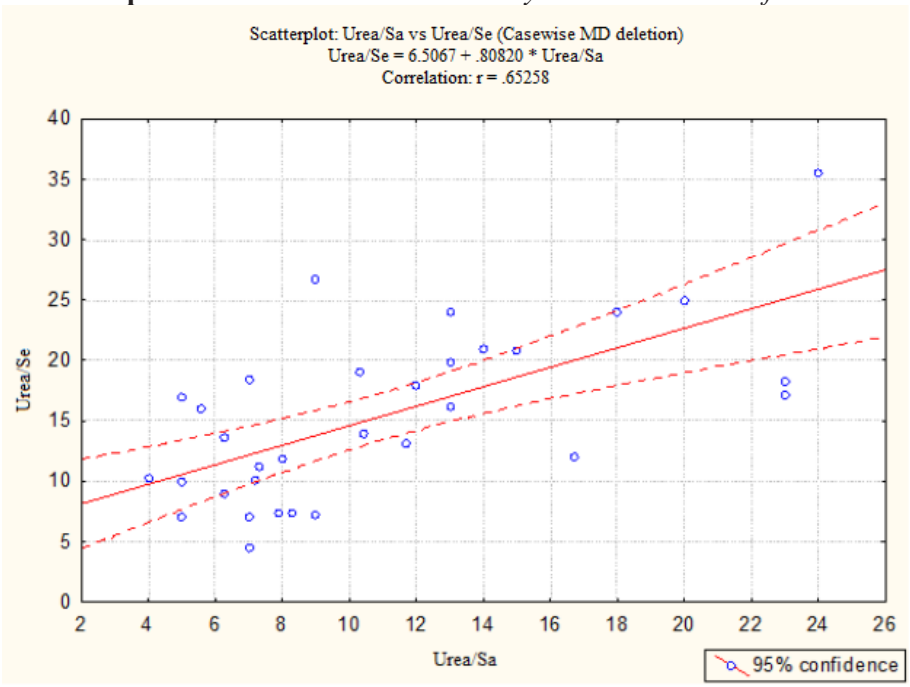
Table 3. *Salivary flow rate in the examined and control group*

T-test for Independent Samples (CKD stat) Note: Variables were treated as independent samples					
	EG	CG	t-value	df	p
mil/min	0.32	0.48	-3.23	50	0.002

*Examined group, **Control group

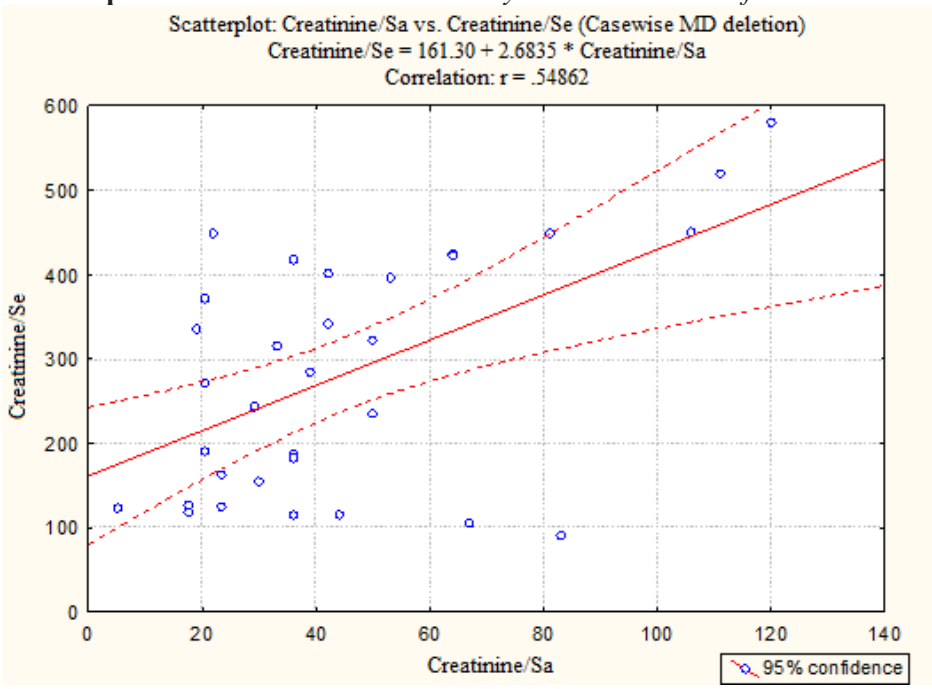
Our results showed a statistically significant positive correlation between salivary and serum levels of urea (Graph 1) and creatinine (Graph 2) in patients with CKD. The mean values of the serum urea in the patients with CKD were 15.4 mmol/L, while the mean values of the serum creatinine in the patients with CKD were 272.59 μmol/L. Pearson's correlation coefficient for urea was r =0.6527, p = 0.000, while for creatinine it was r = 0.5486, p = 0.001.

Graph 1. *Correlation between salivary and serum levels of urea*



*Urea/Sa – salivary urea
*Urea/Se – serum urea

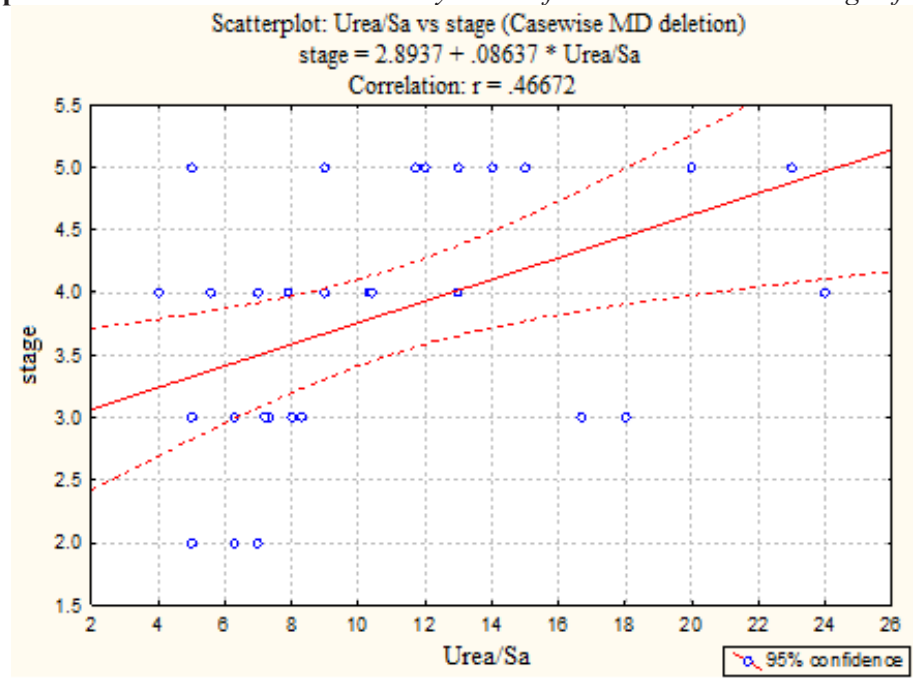
Graph 2. *Correlation between salivary and serum levels of creatinine*



*Creatinine/Sa – salivary creatinine
*Creatinine/Se – serum creatinine

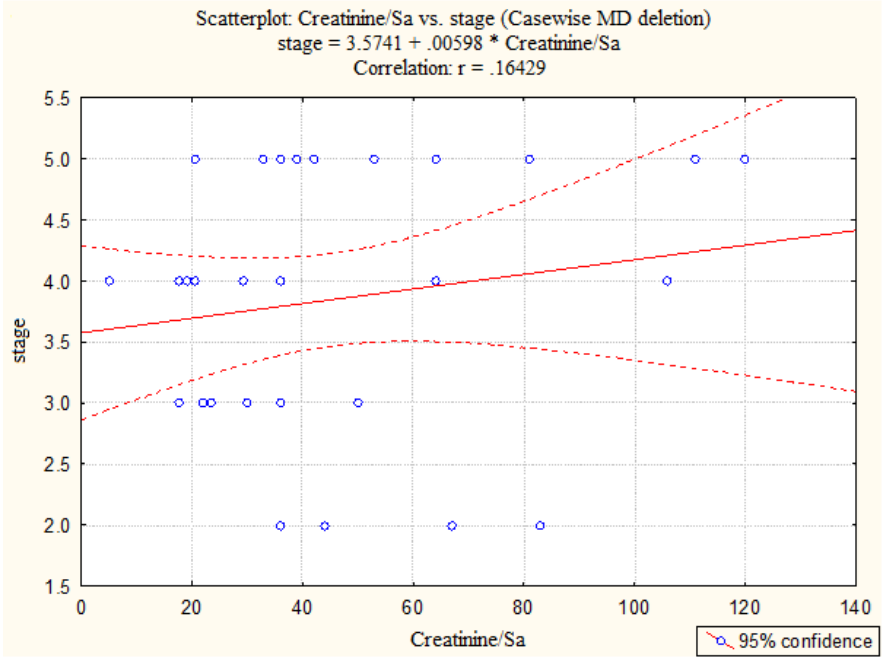
We have also detected a statistically significant positive correlation between the salivary levels of urea and the clinical stage of CKD, r = 0.4667, p = 0.007 (Graph 3). We did not register a significant correlation between the salivary levels of creatinine and the clinical stage of CKD, r = 0.1643, p = 0.369 (Graph 4).

Graph 3 *Correlation between the salivary levels of urea and the clinical stage of CKD*



*Urea/Sa – salivary urea
*Urea/Se – serum urea

Graph 4. *Correlation between the salivary levels of creatinine and the clinical stage of CKD*



*Creatinine/Sa – salivary creatinine
*Creatinine/Se – serum creatinine

DISCUSSION

Chronic kidney disease (CKD) is a common disorder and an important growing public health problem worldwide. Various factors contribute to this increase, including increased prevalence of diabetes and hypertension [27]. Of particular concern is the large number of young individuals who have CKD. Our results showed that the mean age of the participants included in this study was 54.84 ± 17,69, with the youngest patient being only 16 years old. This data confirms the previous statement and emphasizes the importance of the fact that CKD is not a problem only for the elderly population.

Table 1 displays that more than 1/3 of the patients included in this study were in the terminal stage of CKD (kidney failure). These data indicate the need for early diagnosis of kidney diseases, because with the early detection of kidney diseases, the therapy is much more successful, and complications are avoided. Moreover, considering the cost of one dialysis treatment, the early detection of CKD will reduce the financial burden on the already reduced health budget.

The mean values of salivary urea, salivary creatinine, salivary uric acid and salivary albumin, which were statistically significantly higher in patients with CKD, compared to the values of these salivary parameters in healthy subjects, are shown in Table 2. Our results are in accordance with the results obtained by SaiKiran et al. [28], Xia et al. [29], Bilancio et al. [30] and Maciejczyk et al. [31], whose results also indicate statistically higher values of these salivary parameters in patients with CKD, compared to the control group. The significantly higher values of urea, creatinine and uric acid in saliva are actually a reflection of their increased values in the serum. Uric acid, which has increased concentrations in the saliva of patients with CKD, is a powerful non-enzymatic salivary antioxidant and is used as a marker to measure the antioxidant capacity of saliva [11]. Additional clinical trials are needed to determine the diagnostic value of uric acid determination in patients with CKD [32].

Serum albumin in patients with CKD not only does not show higher values, but hypoalbuminemia is often observed in these patients [33]. Therefore, we believe that the higher salivary values of albumin in patients with CKD are due to the altered (increased) permeability of the acinar cells of the salivary glands in these patients.

In Table 3 we emphasized the significantly lower salivary flow rate in the patients with CKD, compared to the control group. The decreased levels of salivary flow rate and the increased levels of urea and creatinine in saliva account for the xerostomia present in patients with CKD. Uremic fetor, that is, the smell of ammonia from the mouth of patients, is a typical symptom in uremic patients, which is due to the increased levels of urea in the saliva and its decomposition into ammonia.

Through Graph 1 and 2 we can observe a statistically significant positive correlation between salivary and serum levels of urea ($r = 0.6527$) and creatinine ($r = 0.5486$) in patients with CKD. In most of the literature data that were available to us, we registered a positive correlation between the concentrations of urea and creatinine in saliva and serum, in patients with CKD [34-36].

Urea, as a small molecule, easily diffuses through the membrane of the acinus cell and enters the salivary secretion by way of ultrafiltration. Unlike urea, creatinine has a larger molecular mass and lower liposolubility, making its diffusion through the membrane of the acinus cell as well as the diffusion between the acinus cells difficult. Therefore, in healthy individuals, the concentration of salivary creatinine is 1/10 of its concentration in serum, and in several studies [37,38] no positive correlation between serum and salivary levels of creatinine was found in control subjects.

We believe that the positive correlations between serum and salivary levels of degradation products in our patients with CKD are due to an increased serum concentration gradient that facilitates ultrafiltration through acinus cells [39]. In addition, when it comes to salivary creatinine, its concentrations are higher in patients with CKD due to alteration of the permeability of the membrane of acinus cells in these patients [10].

In our study, we found a positive correlation between salivary urea concentrations and clinical disease stage in CKD patients (Graph 3), but we did not find a positive correlation between disease stage in these patients and salivary creatinine values (Graph 4). The explanation for the characteristics of urea and creatinine that were highlighted earlier is the reason for the existence of a positive correlation between the stage of the disease and salivary urea as well as the absence of a positive correlation between the stage of the disease and creatinine concentrations in saliva. Our results are

in accordance with the results obtained by Lin et al. [40], who defined that urea levels clearly increase with advancing CKD severity and allow each of stages 3–5 to be distinguished from each other. In contrast to the results for the correlation between salivary urea and CKD stage, our results for the correlation between salivary creatinine and CKD stage are inconsistent with the results of Venkatapathy et al. [38] who determined a negative correlation between salivary creatinine and CKD stage in controls, but a positive correlation between salivary creatinine and CKD stage in cases.

CONCLUSIONS

The salivary values of urea, creatinine, uric acid and albumin are increased in patients with CKD, compared to the values in healthy subjects.

There is a significant correlation between salivary and serum urea and creatinine values in CKD patients, as well as a positive correlation between CKD stage and salivary urea values.

We believe that salivary urea is a valid marker for determining kidney function and a potential salivary marker for screening and monitoring kidney function. Salivary creatinine can be used more frequently in screening programs as a qualitative marker, thus indicating the existence of a disease, more so than as a quantitative salivary marker.

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Резиме

САЛИВАРНИ МАРКЕРИ КАЈ ПАЦИЕНТИ СО ХРОНИЧНА БУБРЕЖНА БОЛЕСТ

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Цел на истражувањето: Да се утврди можноста за користење на плунката како дијагностичка и прогностичка алатка за скрининг и мониторинг на бубрежната функција.

Методи: Ова истражување вклучи 32 испитаници со различен стадиум на хронична бубрежна инсуфициенција (ХБИ) и 20 здрави испитаници за контролната група. Плунката беше колекционирана со методот на исплукување, а истиот ден од испитаниците беше извадена и крв за одредување на серумските концентрации на уреа и на креатинин. Саливарните вредности на уричната киселина, на уреата, на креатининот и на албуминот беа одредени спектрофотометриски, како и серумските концентрации на уреа и на креатинин.

Резултати: Нашите резултати покажаа статистички сигнификантна позитивна корелација меѓу саливарните и серумските нивоа на уреа и на креатинин кај пациентите со ХБИ (Pearson's correlation coefficient за уреата изнесуваше $r = 0,6527$, $p = 0$, додека за креатининот изнесуваше $r = 0,5486$, $p = 0,001$). Детектиравме статистички сигнификантна позитивна корелација меѓу саливарните вредности на уреата и клиничкиот стадиум на ХБИ ($r = 0,4667$, $p = 0,007$). Не регистриравме сигнификантна корелација меѓу саливарните вредности на креатининот и клиничкиот стадиум на ХБИ ($r = 0,1643$, $p = 0,369$).

Заклучок: Саливарната уреа претставува валиден маркер за одредување на бубрежната функција и потенцијален саливарен маркер за скрининг и мониторинг на бубрежната функција. Саливарниот креатинин може да се употреби како квалитативен маркер, кој само ќе укаже на постоење болест.

Клучни зборови: плунка, уреа, креатинин, бубрежна болест, хронична