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Oral and Salivary Changes in Patients with Chronic Kidney Disease

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Abstract

Introduction. Kidney disease is associated with many abnormalities in the oral health status as well as with alterations in salivary flow and composition. The aim of this study was to evaluate and to correlate oral clinical findings, salivary flow (SF) and salivary pH values in patients with chronic kidney disease (CKD) not yet on hemodyalisis treatment, those undergoing hemodialysis and in kidney transplant recipients.
Methods. In a cross-sectional study 90 patients were included. The cohort was composed of three groups: 30 patients with CKD (serum creatinine values under 120 μmol/L-group 1), 30 patients with CKD on hemodialysis (group 2) and 30 kidney transplanted patients (group 3). The control group consisted of 20 healthy individuals. Oral symptoms, signs and lesions: salivary volume, salivary pH and SF of stimulated and unstimulated saliva were evaluated.
Results. Among patients with CKD without dialysis treatment inverse relationship was found between uremic fetor, unpleasant taste and unstimulated SF and also between xerostomia and stimulated SF. Negative correlation between thirst and unstimulated salivary flow was found in both groups, patients with CKD on dialysis and kidney transplant group. Furthermore, in kidney-transplant patients a negative correlation was found between petechiae and SF, while in group of patients with CKD on hemodialysis the same negative correlation was registered between uremic fetor and stimulated SF.
Conclusions. Salivary flow was significantly lower in hemodialysis patients, while the highest was in the kidney-transplant recipients accompanied with improvement in the other oral clinical findings observed in our study.

Key words: hemodialysis, kidney transplantation, oral findings, salivary flow

Introduction

Patients with chronic kidney disease (CKD) often present systemic complications such as anemia, coagulation and platelet function disorders [1]. Some of them manifest oral symptoms and signs [2]. Oral symptoms may be more or less prevalent in the oral mucosa [3,4]. It has been proven that approximately 90% of the patients with CKD have soft tissue changes [5]. Besides changes in the soft tissue, in these patients there is an increased risk of caries which is considered to be a multifactorial disease.
Several studies have reported the connection of the salivary flow with periodontal, dental and oral status in CKD patients [6,7]. It has been also reported that in CKD patients saliva has important protective properties, participating in the maintenance of oral mucosa and hard tissues integrity, that is in the physiological balance within normal condition. Any deviation may influence the condition of the tissues in the oral cavity [8]. Salivary buffer capacity is an important parameter in maintaining pH of saliva, thereby reflecting on the integrity of soft and hard tissue in the oral cavity [9-11].
According to Bots *et al.* [6] any disorder which influences on the established equilibrium of all components in the oral cavity leads to a reduction in salivary flow, which may cause symptoms and signs of xerostomia and atrophic changes on the oral mucosa. It is considered that determination of some biomarkers in saliva can be effective alternative method for monitoring the efficacy of the treatment with dialysis in CKD patients [12]. In that context Blicharz *et al.* [12] believe that saliva sample represents a revolution in diagnostic and therapeutic monitoring strategies in CKD patients and those suffering from other chronic diseases.
Considering these facts the aim of our study was to find the association between salivary flow and oral clinical findings in patients with chronic kidney disease.

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Material and methods

Ninety patients with diagnosed CKD from the University Department of Nephrology, University of Skopje and the eponymous hemodialysis center were included in the study. Complete anamnestic procedure and clinical examination were performed at the University Department of Oral Pathology and Periodontology, and laboratory investigations were performed at the Department of Medical and Experimental Biochemistry in Skopje. Twenty healthy subjects without any kidney disease were included in the control group.

Patients with CKD included in the study were divided into three groups. The first group (group 1) consisted of 30 patients with CKD and serum creatinine level below 120 μmol/L. The second group (group 2) consisted of 30 patients with CKD undergoing hemodialysis, and the third group (group 3) consisted of 30 kidney transplant patients.

Our cohort was predominantly female (52 women) with mean age of 46±14 years. The frequency of hemodialysis was three times per week with duration of four hours per session in the group of patients undergoing hemodialysis (group 2). Kidney transplanted patients (group 2) received standard triple immunosuppressive therapy which include micophenolate mophetil, prednosine and cyclosporine at a daily dose of 100-175 mg (neoral 3-4 mg/kg/day). All subjects were informed about the procedure and agreed to participate in the study. Information about oral health status of all patients included in the study was obtained from the anamnesis and clinical examination. Oral changes were followed on the entire mucosal surface of the oral cavity and were classified into subjective and objective findings.

The anamnestic data gave the following most common subjective oral symptoms and signs: uremic fetor, unpleasant taste, thirst, xerostomia and burning tongue.

Uremic fetor was recorded as a urine-odor breath, and unpleasant taste as a lack of normal perception of different tastes in food. Diagnosis of xerostomia was made based on the patients' report of dry mouth and during oral inspection when dental instrument was sticking to the oral mucosa.

The objective clinical finding based on the examination of the oral mucosa revealed changes and lesions such as: pale mucosa, dry fissured lips, coated tongue, petechiae and ecchymoses, uremic stomatitis and angular cheilitis.

Oral lesions in our study were registered according to acknowledged clinical diagnostic criteria [13,14]. Dry and fissured lips were recorded when smaller or larger squamous formations on mildly erythematous vermilion surface were observed. Coated tongue was recorded as dirty white plaque formations on the dorsal surface with present elongated filiform papillae. Uremic stomatitis was registered as irregular erythematosus areas covered with grayish white pseudomembranes localized on lateral borders and dorsum of the tongue or buccal mucosa accompanied with painful sensations.

In all subjects included in our study, stimulated and unstimulated saliva samples were obtained, and salivary pH and salivary flow were determined. In patients on hemodialysis treatment (group B) saliva samples were taken immediately before the dialysis session, and in the other subjects samples of saliva were collected in the morning before breakfast, according to the spitting method. The collection of saliva started with instruction to the subjects to abstain from smoking, eating, drinking, and tooth brushing for one hour prior collection. All subjects were advised to rinse the mouth with water before the collection of saliva. The collection period lasted for five minutes. Stimulated saliva was collected by using chewing gum.

During preparation of saliva samples, the test tubes were kept on ice. The volume of saliva was determined gravimetrically (assuming 1 g=1 ml) and the pH was determined within five minutes after collection by electrolyte analyzer (Humalyte Plus [5], Human, Germany).

Statistical analysis

The obtained data were statistically analyzed, presented as mean values with standard deviation. The significance of differences in the salivary flow and salivary pH values among all studied groups were assessed by using the Kruskall-Wallis-test. The Mann-Whitney U-test was used to examine the significance of difference between two groups. Correlations between salivary findings and oral changes were performed using the Spearman's rank test. A p-value <0.05 was considered as statistically significant.

Results

The examined groups had different flow rates of saliva, with or without stimulation. As expected, the lowest flow rate of unstimulated saliva was evident in patients undergoing hemodialysis (Table 1). Mann-Whitney test showed that unstimulated salivary flow was significantly

Table 1. Salivary flow and salivary pH in control and examined groups

Laboratory results		Control group	Examined group			p
			Group A	Group B	Group C	
Salivary flow ml/min	Unstimulated	0.54±0.20	0.36±0.09	0.31±0.21	0.37±0.27	p<0.05
	Stimulated	1.90±0.42	0.95±0.31*	0.59±0.35	1.02±0.55	p<0.001
Salivary pH	Unstimulated	7.34±0.05	7.37±0.19	7.26±0.35	7.32±0.47	NS
	Stimulated	6.78±0.32	6.88±0.16	6.91± 0.35	6.72±0.38	NS

* Mann-Whitney A/B p<0.05; NS = not significant

lower (p<0.001) in both, the group A (patients on predialysis phase) (0.36±0.09 ml/min) and group B (patients on hemodialysis) (0.31±0.21 ml/min) when compared to the control group (0.54±0.20 ml/min).
There was no statistically significant difference in pH values of stimulated and unstimulated saliva among examined and control groups in our study.
Furthermore, the obtained data from laboratory findings of stimulated saliva indicated that patients on hemodialysis had the lowest salivary flow rate, and significant difference between the groups for flow rate of stimulated saliva was found (p<0.001).
Additionally, significant difference (p<0.001) in stimulated salivary flow rate between group B (lower) versus other groups (group A, group C and control group) (higher), and significant difference (p<0.01) between group A (lower) and control group (higher) was found.
The obtained results for the correlation between oral and salivary flow changes are shown in Table 2 and Table 3.
In pre-dialysis patients (group A) a negative correlation between uremic fetor and unstimulated salivary flow (r =-0.686; p<0.001) was found, which was not found in patients on hemodialysis (group B) nor in kidney transplant patients (group C).

Table 2. Correlation between unstimulated salivary flow and oral changes in patients with CKD

Oral symptoms, signs, changes and lesions	Salivary flow rate of unstimulated saliva					
	Group A		Group B		Group C	
	Spearman Rank Test	*p*	Spearman Rank Test	*p*	Spearman Rank Test	*p*
Uremic fetor	*r* =-0.686	<0.001	*r* =-0.352	NS	*r* =0.184	NS
Unpleasant taste	*r* =-0.686	<0.001	*r* =-0.70	NS	*r* =0.084	NS
Thirst	*r* =-0.718	<0.001	*r* =-0.617	<0.001	*r* =-0.075	NS
Xerostomia	*r* =-0.533	<0.01	*r* =-0.512	<0.01	*r* =-0.283	NS
Burning tongue	*r* =- 0.046	NS	*r* =-0.639	<0.001	*r* =0.046	NS
Dry, fissured lips	*r* =-0.087	NS	*r* =0.014	NS	*r* =-0.309	NS
Coated tongue	*r* =-0.224	NS	*r* =0.215	NS	*r* =-0.010	NS
Angular cheilitis	*r* =-0.759	<0.001	*r* =-0.165	NS	*r* =-0.313	NS
Pale mucosa	*r*=0.107	NS	*r*=0.105	NS	*r*=0.108	NS
Petechiae/ecchymosemoses	*r*=-0.268	<0.05	*r*=-0.381	<0.001	*r*=-0.228	<0.05
Uremic stomatitis	*r*=-0.034	NS	*r*=-0.062	NS	*r*=-0.025	NS

Table 3. Correlation between stimulated salivary flow and oral changes in patients with CKD

Oral symptoms, signs, changes and lesions	Salivary flow rate of stimulated saliva					
	Group A		Group B		Group C	
	Spearman Rank Test	*p*	Spearman Rank Test	*p*	Spearman Rank Test	*p*
Uremic fetor	*r* =-0.277	<0.01	*r* =-0.300	<0.001	*r* =-0.240	<0.05
Unpleasant taste	*r* =-0.188	NS	*r* =-0.120	NS	*r* =-0.084	NS
Thirst	*r* =-0.121	NS	*r* =-0.115	NS	*r* =-0.117	NS
Xerostomia	*r* =0.092	NS	*r* =0.008	NS	*r* =-0.157	NS
Burning tongue	*r* =-0.119	NS	*r* =-0.121	NS	*r* =-0.125	NS
Dry, fissured lips	*r* =-0.218	<0.05	*r* =-0.255	<0.05	*r* =-0.206	<0.05
Coated tongue	*r* =-0.160	NS	*r* =-0.158	NS	*r* =-0.120	NS
Angular cheilitis	*r* =-0.128	NS	*r* =-0.119	NS	*r* =-0.121	NS
Pale mucosa	*r* =-0.101	NS	*r* =-0.107	NS	*r* =-0.115	NS
Petechiae / ecchymoses	*r* =-0.405	<0.001	*r* =-0.398	<0.001	*r* =-0.348	<0.001
Uremic stomatitis	*r*=-0.034	NS	*r* =-0.049	NS	*r* =-0.055	NS

Furthermore, a negative correlation between unpleasant taste and unstimulated salivary flow (r=-0.686; p<0.001); was found in the group A, nor in the other two groups.
Moreover, we found a negative correlation between thirst and unstimulated salivary flow in group A (r=-0.718; p<0.001) and group B (r=-0.617; p<0.001). In groups A and B we also found a negative correlation between xerostomia or oral dryness and unstimulated salivary flow.
However, the correlation between unstimulated salivary flow and burning tongue did not reach statistically significant level in patients from group A, while in patients from group B burning tongue negatively correlated with unstimulated salivary flow (r =-0.639; p<0.001).
In all of the three studied groups, a significant correlation between angular cheilitis and unstimulated salivary flow was found only in patients of group A (r=- 0.759; p<0.001).
There was no correlation between unstimulated salivary flow with dry fissured lips, coated tongue, pale mucosa and uremic stomatitis in either of the examined groups.
Furthermore, in our study we found a negative correlation between petechiae and ecchymoses with unstimulated salivary flow in all examined groups. In kidney-transplant patients (group C) with unstimulated salivary flow we found a negative correlation between petechiae and ecchymoses, which was not the case between the other oral changes.

As shown in table 3, stimulated salivary flow was negatively correlated with uremic fetor (r=-0.277; p<0.01), dry fissured lips (r=-0.218; p<0.05), petechiae and ecchymoses (r=-0.405; p<0.001) in pre-dialysis patients from group A. Similarly, a negative correlation was found between stimulated salivary flow and the same listed oral changes in hemodialysis patients from group B and kidney- transplant patients from group C.

Discussion

The improved health care, pharmacological progress and extended life span have increased the number of patients living with chronic kidney disease seeking dental treatment. In most of them a wide range of oral manifestations as gingivitis, xerostomia, uremic fetor, pale mucosa etc. were observed [15,16]. Here, according to Bots *et al*. [6] the saliva has a crucial role. Changes in the flow of saliva, pH values and biochemical composition are reflected on the oral clinical finding. In this study, patients with CKD had reduced flow of stimulated and unstimulated saliva, compared to the control group. In group A (patients with serum creatinine 120 μmol/L) there was a negative correlation between uremic fetor, unpleasant taste, thirst, xerostomia and unstimulated salivary flow. Similarly, in group B (hemodialysis patients) a negative correlation between thirst, xerostomia, burning tongue and unstimulated salivary flow was found. Thus, we assume that thirst in hemodialysis patients is a result of fluid restriction implemented in order to prevent fluid overload between dialysis sessions, and consequently to prevent the occurrence of hypertension. The presence or occurrence of thirst in patients in pre-dialysis phase and patients on hemodialysis might be explained as a consequence of the present hyposalivation; in our study confirmed by the negative correlation between thirst and unstimulated salivary flow in groups A and B (r=-0.718, p<0.001; r=-0.617, p<0.001). Hence, it means that reduction of the salivary flow in groups A and B, results with the emergence of thirst. Abuleo *et al*. [17] reported high levels of serum sodium, angiotensin II, rapid rise of urea in serum, as well as psychological factors as possible reasons for thirst in CKD patients. In patients with kidney transplantation (group C), although they had nearly the same values of unstimulated saliva as patients from group A (0.37±0.27 ml/min vs 0.36 ml/min), there was no association between thirst and their average amount of unstimulated salivary flow (r=0.695; p>0.05). The authors believe that the reason for presence of thirst in kidney-transplant patients is of a complex nature. In fact, despite the determined hyposalivation, dominant role belongs to the synergistic side effect of the maintenance immunosuppressive and corticosteroid therapy [3,6,11].

According to Hamid *et al*. [1], except thirst, xerostomia appears as a quite frequent oral symptom in CKD patients. On the other side, Dirschabel *et al*. [18] registered a high prevalence of oral lesions, such as xerostomia and coated tongue in hemodialysis and renal transplant patients.

Our experience showed that xerostomia and thirst are the most common oral discomforts, which patients in pre-dialysis phase and patient undergoing haemodialysis face. Bots *et al*. [6] after a two-year period of monitoring of CKD patients, showed that the prevalence of xerostomia and thirst remained the same quantity during the period of follow-up in patients on dialysis treatment. In contrast, in the same study, patients who carried out renal transplantation were characterized with decreased oral dryness, thirst and increased salivary flow. In line with the previous observation, in our study we did not find any statistically significant correlation between oral dryness with either stimulated or unstimulated salivary flow (r=-0.157; r=-0,283; p>0.05) in renal transplant patients. However, we found a negative correlation between unstimulated salivary flow and xerostomia (r=-0.533; r=-0.512; p<0.01) between the groups A and B. Besides the reduced salivary flow in patients with CKD, we assume that oral dryness could further exacerbate by the applied medicament therapy. It has to be pointed out that patients included in this study, despite their main immunosuppressive regimen, were treated with ACE-inhibitors, antidepressants and sedatives.

On the other side, in this study an inverse correlation between unpleasant taste and unstimulated salivary flow in pre-dialysis patients from group A was found. Actually, the reduced salivary flow causes the oral dryness, which initiates a changed taste perception in these patients. It is well-known that the sensitivity of taste perceptions is altered for all four basic types of flavor, due to insufficient solubility which reacts to oral chemoreceptors, causing an unpleasant metallic taste and the taste perception is impaired in all uremic patients, regardless of the type of treatment [17].

In our study, an inverse correlation between uremic fetor and unstimulated salivary flow in patients from group A (r=-0.686 p<0.001) and between uremic fetor and stimulated saliva in patients from groups A (r=-0.277 p<0.01) and B (r=-0.240 p<0.05) was found. Therefore, we think that the reduced salivary flow in this category of patients abounded with urea metabolites, especially ammonia that could be accepted as a main factor for the occurrence of uremic fetor. Keles *et al*. [19] and Martins *et al*. [20] reported identical findings. However, this correlation is interpreted differently by Mason *et al*. [21]. In fact, along with the reduction of salivary flow there is an increase in the concentration of uric acid. So, in patients with reduced salivary flow and subsequently increased concentration of uric acid in saliva, an increased presence of uremic fetor may occur. In CKD patients, despite previously mentioned reasons, the poor oral hygiene and dental plaque accumulation, due to their lack of motivation and less priority to maintain oral health, are accepted as additional factors that emphasize the uremic fetor.

Among all of our studied groups, a negative correlation between salivary flow of unstimulated saliva and the burning tongue in hemodialysis patients from group B was found. We assume that the major reason for appearance of burning tongue is dehydrated oral mucosa. The reduced salivary flow affects the vulnerability of oral mucosa, making it too sensitive, thereby emphasizing the symptom of burning sensation. Additionally**,** the dry and vulnerable mucosa, insufficient humidity in mouth and lost elasticity, make the oral mucosa to be easily traumatized, which is clinically manifested by occurrence of petechiae and ecchymoses. Petechiae and ecchymoses of oral mucosa, in all of our studied groups were negatively associated with unstimulated and stimulated flow of saliva ($p<0.001$). These results do not match with those of Skorecki *et al*. [22], Kerr *et al*. [23] and Ziccardi *et al*. [24]. According to these authors petechiae and ecchymoses are common oral clinical finding seen in patients with CKD, as a result of altered platelet aggregation in conditions of uremia. Kho *et al*. [25] and Chuang *et al*. [26] claim that reduced salivary flow, heparin and other anticoagulants that patients on dialysis receive, are the primary reason for petechiae and ecchymoses. In agreement with these data and the results from the current study, we think that all previously mentioned reasons may mutually contribute to the occurrence of petechiae and ecchymoses in patients with CKD.

Furthermore, in this study we found a negative correlation between angular cheilitis and unstimulated salivary flow in patients from group A. Unfortunately, in the literature there are poor data and hence, we could not compare our findings. In support of our findings are the results reported by Klassen *et al*. [27]. They found a prevalence of 4% angular cheilitis in dialysis patients. On the other side, in the studies of Obry *et al*. [28] and Holmstrup *et al*. [29] an association between angular cheilitis and anemia and candidiasis was reported. However, we consider that with the reduced amount of saliva and lost humidity of oral epithelium there is a reduced local defense mechanism in patients with CKD. We confirmed in our study that the lower flow of saliva impaired keratinization and decreased immunity, and created an ideal base for development of fungal or bacterial infection on the corner of the lips, especially in the immunocompromised CKD patients.

In our study, flow rate of both stimulated and unstimulated saliva was not associated with coated tongue, uremic stomatitis and pale mucosa among all participants. In hemodialysis patients salivary flow of unstimulated saliva was inversely associated with xerostomia, thirst, burning tongue, petechiae and ecchymoses. On the other side, salivary flow of unstimulated saliva was inversely associated with thirst, uremic fetor, unpleasant taste and angular cheilitis, in pre-dialysis patients, while in kidney-transplant patients, petechiae and ecchymoses salivary flow of unstimulated saliva was not associated with any other oral changes.

Conclusions

In conclusion, the reduced salivary flow in patients with CKD negatively affects their oral health, resulting in occurrence of many oral symptoms, changes and lesions. In this study, salivary flow rates were found to be the lowest in patients on hemodialysis, and the highest in kidney-transplant patients. Hence, renal transplantation as a treatment of choice in patients with irreversible renal failure not only restores renal function, but has also influence on increased flow of saliva and reduced incidence of oral changes.

Conflict of interest statement. None declared.

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