

ORAL FINDINGS IN END-STAGE RENAL DISEASE

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Abstract

The aim of the study was to analyse and compare the most frequent clinical oral symptoms, signs and lesions at end-stage renal disease (ESRD), before kidney transplantation (BKT) and after kidney transplantation (AKT). A total of 35 subjects with ESRD were included, 19 in group A (BKT) and 16 in group B (AKT). Oral lesions were classified according to referent clinical diagnostic criteria: Serum albumins, urea, creatinine and salivary urea, creatinine uremic acid were determined by standard biochemical spectrophotometric methods (Human, Germany). For serum albumin concentration measurement (g/L) the method of bromocresol green assay was used while serum and salivary uric acid determination ($\mu\text{mol/L}$) was performed according the uricase/PAP method. Serum creatinine concentration was measured ($\mu\text{mol/L}$) with the Jaffe kinetics method, without deproteinization. Oral signs, symptoms and lesions were higher in group A: metallic taste (O.R. = 6.61/ \pm 95% CI : 1.13 < O.R. < 38.69), dry mouth (O.R. = 30/ \pm 95% CI : 3.15 < O.R. < 285.71), uremic stomatitis (O.R. = 6.5/ \pm 95% CI : 1.47 < O.R. < 28.80 and coated tongue (O.R. = 11.73/ \pm 95% CI : 2.31 < O.R. < 59.54). On the other hand, in group B, gingival enlargement (O.R. = 59.5/ \pm 95% CI : 7.41 < O.R. < 478.05) was more common. High statistically significant differences were recorded between group A and B for dry mouth and gingival enlargement ($p > 0.001$). Blood urea, creatinine and albumin levels, as well as salivary urea creatinine and uraemic acid values, were significantly higher in group A. Chances of the appearance of all symptoms, clinical signs and lesions, except gingival enlargement, were greater in group A as against group B. Some of our findings correspond with the stage of the disease and some with the use of medicaments in treatment.

Key words: End-stage renal disease, Kidney transplantation, Oral sign, Oral lesion.

Introduction

Chronic renal failure (CRF) could be defined as a progressive and irreversible glomeru-

lar filtration rate (GFR) decrease, resulting in an increase of serum creatinine and blood nitrogen-containing compounds [1, 2]. Urea levels

are increased once GFR is decreased to 5–10% of normal. Expectedly, disordered GFR and uraemia onset are associated with physiological and biochemical alterations in CRF.

CRF subjects are associated with systemic complications such as anaemia, and platelets and coagulation factor abnormalities [3]. In addition, some of them present with oral cavity symptoms and signs [4]. These symptoms could be frequent or rare pathological conditions of the oral mucosa [1, 5]. Thus, approximately 90% of patients with CRF experience oral signs and symptoms distressing the soft or hard tissues of the oral cavity [6]. Hamid et al. [3] points to xerostomia, stomatitis, periodontal affection and maxillary radiography changes as most frequent oral manifestations.

As dental healthcare providers are very often faced with such conditions in CRF subjects on dialysis, the aim of our study was to analyse and compare the most frequent clinical oral symptoms, signs and lesions in dialysis patients at the end stage of the underlying disease or before kidney transplantation (BKT) and after kidney transplantation (AKT) as a best treatment option for renal replacement therapy.

Material and methods

A total of 35 subjects with CRF were included in this study, 19 of them in the end stage before kidney transplantation (BKT – group A) and 16 after kidney transplantation (BKT – group B). Of the total of 35 subjects, 23 were males and 12 females. Group A consisted of 12 males and 7 females, mean age 44.05 ± 12.36 years, and group B included 11 males and 5 females, mean age 50.38 ± 7.82 . All study participants were recruited from the Department for Nephrology at the University Clinical Centre in Skopje, Macedonia.

Group B included only subjects with a serum creatinine level $< 120 \mu\text{mol/L}$ anticipated as with normal renal function. Group A comprised subjects undergoing haemodialysis therapy three times a week on calcium carbonate (CaCO_3) tablets 2–4 g a day as the most frequently used phosphate binder therapy. Group B subjects were taking Cyclosporine in a daily dose of 125–250 mg (Neoral; 2–4 mg/kg, Novartis, Switzerland).

Before enrolment, each participant consented to a protocol reviewed and approved by

the Medical Ethics Committee at the Faculty of Dentistry, Skopje, Macedonia.

Demographic features, time of haemodialysis onset or period since kidney transplantation, clinical and laboratory findings were evaluated.

Oral clinical signs, symptoms and lesions were registered as follows: uraemic fetor, metallic taste in the mouth, dry mouth, uraemic stomatitis, dry and cracked lips, coated tongue, and gingival enlargement. The specific oral expressions of the overall oral mucosa and mouth were classified according to subjective and objective findings. Uraemic fetor was reported as a urine-like or acetone-like odour of the breath, and metallic taste as loss of normal detection of different food tastes. When dry mouth was reported, patients complained about difficulties in taking food, and speech problems; during oral inspection fingers stuck to the oral mucosa. Salivary flow was not assessed.

Oral lesions were classified according to referent clinical diagnostic criteria [7, 8]. Uraemic stomatitis exhibited irregular and mild erythematous surfaces coated with greyish white pseudo membranes located on the dorsal and tongue edge surfaces, and accompanied with painful sensations. Dry and cracked lips displayed smaller or larger squamous formations on a mildly erythematous vermilion surface.

On the dorsum, the tongue was coated and had a dirty white plaque formation that could be removed with dental instruments. Elongated filiform papillae were disclosed. Marginal gingiva and interdental gingival papillae were enlarged, and light reddish or severe gingival bleeding could easily be provoked.

A venous blood sample was investigated for urea, creatinine and albumins, while mixed saliva was used for urea concentration, creatinine, albumins and uric acid. After collection, saliva was homogenized by vigorous one-minute mixing using a vortex mixer, and then centrifuged for 10 minutes/10 000 g at room temperature in order to eliminate cellular debris. Supernatant liquid was investigated for assessing the above-mentioned components. The overall time of collection and processing of saliva samples was approximately 30 minutes, during which time test tubes were kept on ice.

Using the method of spitting, mixed saliva samples from study group A were obtained before the haemodialysis session, and from

group B before taking breakfast. Both groups were advised not to smoke, drink or brush teeth for one hour before saliva collection. The collection process was approached with an instruction to rinse the mouth with water, and was performed for 5 minutes in special test tubes, for 30 seconds each.

Serum albumins, urea, creatinine and salivary urea, and creatinine uraemic acid were determined in an automated biochemical analyser (Chem Well, Awareness Technology, Inc. USA), by standard biochemical spectrophotometric methods (Human, Germany). For serum albumin concentrations measurement (g/L) the method of bromocresol green assay was used while serum and salivary uric acid determination ($\mu\text{mol/L}$) was performed according to the uricase/PAP method. Serum creatinine concentration was measured ($\mu\text{mol/L}$) with the Jaffe kinetics method, without deproteinization.

A descriptive statistical analysis was performed for series with numeric values. Differences of laboratory blood and saliva findings between both groups were tested by the *t*-test for independent samples. Differences in symptoms, signs, alterations and lesions between the study groups were tested by the Pearson Chi-square

test. The risk of certain symptoms, signs and lesions onset was measured by Odds Ratio. Values $p < 0.05$ indicate a significant finding. The statistical programme used was Statistica 7.1.

Results

A total of 35 individuals divided into two groups were included in our investigation. Group A consisted of 19 (54.29%) dialysis subjects before kidney transplantation and group B of 16 (45.71%), after kidney transplantation (Table 1). There was no significant sex difference. Group A mean age was 44.05 ± 12.36 , (range 27–66 years). The mean age in group B was 50.38 ± 7.82 years (range 38–62). Dialysis vintage in group A varied from 45.32 ± 23.39 months. The minimal time was 9 up to 98 months, while the time of transplantation in group B varied in the interval of 44.94 ± 15.19 months, and the minimal time was 17 up to 71 months. Salivary and blood values of urea and creatinine, albumin and salivary uraemic acid in both groups are shown in Table 1. Blood urea, creatinine and albumin levels, as well as salivary urea creatinine and uraemic acid values, were significantly higher in group A compared to group B.

Table 1

Blood and salivary biochemical findings in groups A and B according to sex and age

	Group A		Group B		t	p
	N(%)	Mean \pm SD	N(%)	Mean \pm SD		
Male	12 (63.16%)		11 (68.75%)			
Female	7 (36.84%)		5 (31.25%)			
Age		44.05 ± 12.36		50.38 ± 7.82	-1.77	NS
Blood findings						
Urea		26.47 ± 5.14		9.94 ± 5.73	8.99	***
Creatinine		628.42 ± 265.65		115.25 ± 13.44	7.70	***
Albumins		4.68 ± 10.6		3.19 ± 5.4	5.11	***
Salivary findings						
Urea		15.16 ± 5.21		9.54 ± 4.13	3.49	**
Creatinine		188.93 ± 59.72		101.75 ± 122.65	2.74	**
Uremic acid		430.63 ± 196.48		193.11 ± 225.77	3.33	**

P < 0.01**; p < 0.001***

Symptoms, signs and lesions data distribution for groups A and B are given in Table 2.

Uremic foetor, dry mouth and cracked lips did not show statistically significant differences between the two groups (Fig. 1). Metallic taste and uraemic stomatitis between both showed

low significance ($p < 0.05$), but coated tongue showed temperately significant (Figs. 2a, 2b, 3). High statistically significant differences were record between group A and B in dry mouth and gingival enlargement.

Table 2

Differences in symptoms, signs and lesions between groups A and B

	Pearson Chi-square	df	p
Symptoms, signs and lesions			
Uremic foetor	1.56	1	NS
Metallic taste	5.02	1	*
Dry mouth	13.20	1	***
Alterations and lesions			
Uremic stomatitis	6.56	1	*
Dry and cracked lips	0.22	1	NS
Coated tongue	10.15	1	**
Gingival enlargement	20.74	1	***

$p < 0.05^*$; $p < 0.01^{**}$; $p < 0.001^{***}$



Fig. 1 – Dry and cracked lips in patient BKT

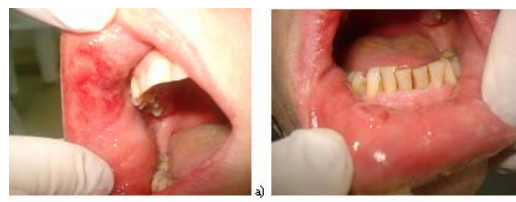


Fig. 2 – Uremic stomatitis in patients BKT on:
a) buccal mucosa; b) labial mucosa



Fig. 3 – Coated tongue in BKT participants

Table 3 presents data distribution regarding the risk of the appearance of oral symptoms, signs and lesions in both groups. Group A participants experienced a 6.61 times higher chance of having a metallic taste (O.R. = 6.61/ \pm 95% CI : 1.13 < O.R. < 38.69) than those in group B. Dry mouth appeared 30 times more frequently in group A compared to group B (O.R. = 30/ \pm 95% CI : 3.15 < O.R. < 285.71).

Table 3

The risk for appearance of oral symptoms, signs and lesions among participants between groups A and B

	Group A	Group B		
	Cases (%)	Cases (%)	OR	95% CI
Uremic foetor	18 (51.43)	13 (37.14)	4.15	0.39–44.57
Metallic taste	17 (48.57)	9 (25.71)	6.61	1.13–38.69
Dry mouth	18 (51.43)	6 (17.14)	30	3.15–285.71
Uremic stomatitis	13 (37.14)	4 (11.43)	6,5	1.47–28.80
Dry and cracked lips	8 (22.86)	8 (22.86)	0.73	19–2.77
Coated tongue	16 (45.71)	5 (14.29)	11.73	2.31–59.54
Gingival enlargement	2 (12.50)	17 (89.47)	59.5	7.41–478.05

OR = Odds ratio, 95%, CL = 95% confidence limits

Uraemic stomatitis in group A was 6.5 times higher (O.R. = 6.5/ \pm 95% CI : 1.47 < O.R. < 28.80) as compared to group B. In group A the chance of having a coated tongue

was 11.73 times higher than in group B (O.R. = 11.73/ \pm 95% CI : 2.31 < O.R. < 59.54). On the other hand, among group B subjects results point out the 59.5 times greater chance of having

gingival enlargement (O.R. = $59.5 \pm 95\%$ CI : $7.41 < \text{O.R.} < 478.05$) than those in group A. Differences between groups A and B concerning metallic taste, uraemic stomatitis and coated tongue are statistically significant.

In group A the chances of uremic fetor were 4.15 times higher (O.R. = $4.15 \pm 95\%$ CI : $0.39 < \text{O.R.} < 44.57$), while dry and cracked lips in group A were only 0.73 times higher compared to group B (O.R. = $0.73 \pm 95\%$ CI : $0.19 < \text{O.R.} < 2.77$). Differences between the groups associated with uraemic fetor and dry and cracked lips were not significant.

Discussion

Decreased glomerular filtration in CRF leads to a collection and retention of different products which have an impact on different organs and systems. Expectedly, the clinical signs and symptoms are related to the kind and level of the impaired renal function.

Uraemic stomatitis, candidomycotic infection, dentition and alveolar bone defects, tongue and salivary gland lesions can be very frequent [9]. As a result of anaemia, uraemic patients also display a pale oral mucosa [6, 8]. Yet mouth symptoms and lesions are not related only to renal insufficiency, they could also be due to the use of medications after kidney transplantation [10]. Our investigation suggests that the presence of symptoms, signs and lesions was significantly higher among group A participants compared to those from group B. Also, we showed twice or thrice higher serum urea values, but not salivary ones. Analysis of the urea values in group B revealed slightly increased values. Salivary urea concentration and the degradation into ammoniac is the reason for oral fetor, which is typical of every uraemic patient. These findings are in line with those reported by De la Rosa-García [11] in a study dealing with end-stage renal failure.

Our results revealed that a metallic taste was present among 26 participants from both groups (74.29%). The symptom prevailed in group A, 17 (48.57%) compared to group B – 9 (25.71%). According to the best of our knowledge, the final metabolic nitric products, the high level of ammoniac and salivary biochemical alterations are continuous irritators of the oral cavity which causes changes in taste percep-

tion. Several oral lesions are typical of a certain stage of renal disorders, so in patients on dialysis a metallic taste is more frequent, while in those with kidney transplantation gingival enlargement is the more prevalent lesion [10]. Our assumption is that the additional reason for a metallic taste in group A was the increased concentration of albumins, and changes of the Salivary pH, as confirming the report from [12].

The quality of taste perception is impaired for all four basic taste perceptions in patients with chronic renal failure. Additionally, the taste perception is impaired in all uraemic patients regardless of whether or not they are on haemodialysis.

A dry mouth is a very frequent symptom in patients with chronic renal failure. In our study dry mouth was present in 18 group A subjects (51.43%) and 6 (17.14%) in group B. We consider this has to be due to the salivary glands' impaired function, fibrosis and atrophic changes to the glandular parenchyma, and dehydration and mouth breathing which was prevalent in group A patients. On the other hand, a dry mouth could be responsible for a coated tongue, accumulation of dental plaque and gingival enlargement [3, 13]. We suppose that the dry mouth may be an additional reason for the unpleasant taste and odour that is more prevalent in group A. On the other hand, Postorino [14] reported that a dry mouth is associated with a metallic taste among patients with terminal stage chronic renal failure with diabetes.

Uraemic stomatitis presented as superficial white plaque on an erythematous surface was localized at the dorsal side of the tongue and on the buccal oral mucosa. In group A, it was evidenced in 13 patients (37.14%), and in 4 from group B. A soft mushy cover in the form of pul-taceous erythema with a white linear plaque was evidenced in more than two thirds of patients in group A. This is due to tissue irritation by ammoniac or high levels of salivary urea [14, 15].

According to our experience and knowledge, this clinical finding is probably related to uraemic acid crystals deposited on the epithelial surface after water component evaporation or after a salivary flow decrease which is very common. Uraemic lesions were more frequent in group A than in group B, where Salivary uraemic acid values were higher (O.R. = $6.5 \pm 95\%$ CI : $1.47 < \text{O.R.} < 28.80$).

According to Antoniadis et al. [16] uraemic stomatitis is manifested in the advanced stage of CRF, which we confirmed in our findings. A coated tongue prevailed in group A (45.71%) compared to group B (14.29%). Hyperplastic filiform papillae, poor oral hygiene, and decreased salivary flow are responsible for such clinical findings. De la Rossa [11] in his study evidenced coated tongue among 22.2% of patients after kidney transplantation. However, in our study dry lips were identically frequent in both investigated groups.

Literature data reveal that beside oral mucosa, alterations, periodontitis, severe gingivitis, or an initial form of periodontal disease could be also found among patients with renal insufficiency [17].

Gingival enlargement was most frequent in group B. Marginal gingiva and the most peripheral parts of the attached gingiva disclosed mild inflammation, paleness, thick, solid, not bleeding on probing. Interdental papillae presented thickening and enlargement exceeding the interdental space. Periodontal pockets were deep due to gingival enlargement and apical epithelial migration as well. This clinical finding is in direct relation to the cyclosporine therapy in patients with kidney transplantation [18]. Cyclosporine influences the collagen fibres and the connective tissue, causing hypertrophy and hyperplasia. Identical findings are reported in the investigation of [19, 10]. Our findings are in consensus with [10, 18, 19].

Gingival fibrous hyperplasia being induced by cyclosporin causes gross plaque accumulation in the deep pockets which can hardly be removed due to their depth and inaccessibility [19, 20].

Conclusion

Chances of the appearance of all symptoms, clinical signs and lesions, except gingival enlargement, were greater in group A than in group B. Our findings correspond with the severity of clinical signs, as well as the use of medicaments in treatment of the disease. The treatment of renal diseases is related to many risks and complications, including a high risk of pathological oral changes in different phases of disease. With the aim of decreasing the appearance of certain oral manifestations, consultation with a dentist is necessary to prevent oral ill-health and to improve the quality of life for renal patients.

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Резиме

ОРАЛНИ ПРОМЕНИ ВО КРАЕН СТАДИУМ НА БУБРЕЖНИ ЗАБОЛУВАЊА

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Целта на оваа студија е да ги евидентираме и да ги споредиме најчестите клинички орални симптоми, знаци и лезии кај пациенти со краен стадиум на бубрежна инсуфици-

енција пред и по трансплантацијата. Од вкупно 35 пациенти со краен стадиум на бубрежна инсуфициенција, 19 беа пациенти пред трансплантација (група А) и 16 по спроведената трансплантација (група Б). Оралните лезии беа класифицирани според референтни клинички критериуми. Серумските албумини, уреа, креатинин и саливарната уреа, креатинин, уремичната киселина беа одредувани со примена на стандардни биохемиски спектрофотометриски анализи (Human, Germany). Методот на бромкрезол зелено е применет за одредување на серумските албумини (g/L), додека одредувањето на серумската и саливарната уремична киселина ($\mu\text{mol/L}$) е спроведено со уриказа/ПАП метод. Со примена на Jaffe кинетичкиот метод без депротеинизација беше одредена концентрацијата на серумскиот креатинин ($\mu\text{mol/L}$). Оралните знаци, симптоми и лезии беа позастапени во групата А: метален вкус (O.R. = 6,61/ \pm 95% CI : 1,13 < O.R. < 38,69), сува уста (O.R. = 30/ \pm 95% CI : 3,15 < O.R. < 285,71), уремичен стоматит (O.R. = 6,5/ \pm 95% CI : 1,47 < O.R. < 28,80 и обложен јазик (O.R. = 11,73/ \pm 95% CI : 2,31 < O.R. < 59,54). Од друга страна, кај пациентите во групата Б, гингивалното зголемување (O.R. = 59,5/ \pm 95% CI : 7,41 < O.R. < 478,05) беше поприсутно. Висока статистичка сигнификантност на разликите е евидентирана помеѓу групата А и Б за сува уста и гингивално зголемување ($p > 0,001$). Уреа во крв, ниво на креатинин и албумин како и саливарната уреа, креатинин и уремична киселина беа сигнификантно повисоки во групата А. Шансите за појава на сите клинички знаци, симптоми и лезии со исклучок на гингивалното зголемување се поголеми во групата А, наспроти групата Б. Некој од нашите наоди кореспондираат со стадиумот на болеста, а некој се последица на употреба на лекови кои се применуваат во третманот на болеста.

Клучни зборови: бубрежна инсуфициенција, трансплантација на бубрег, орални знаци, орални лезии.