Aim: To make comparative evaluation of objective oral clinical findings and subjective oral symptoms in patients with chronic renal failure (CRF) undergoing various therapeutic treatments, and to find possible link between subjective symptoms and objective clinical findings.

Material and Methods: We examined 90 patients with CRF, divided into 3 groups: patients with CRF undergoing haemodialysis, patients with CRF without haemodialysis and serum creatinine <120μmol/L, and patients with renal transplantation. Swab for Candida albicans was taken from oral mucosa. Oral changes were followed on the entire mucosal surface of the oral cavity and were classified into subjective and objective findings.

Results: Certain oral changes showed a predisposition to a particular group of patients, such as petechiae and ecchymoses in the dialysis group and gingival enlargement in the transplant group. Coated tongue, thirst, pale oral mucosa and dry fissured lips were the most frequent oral symptoms and changes among all CRF patients independently the study group. Significant association was found between xerostomia and coated tongue, as well as between unpleasant taste and coated tongue in all the studied patients.

Conclusion: The stadium and consequently severity of CRF, as well as the type of treatment, have influenced the severity of oral clinical findings.

Keywords: Chronic Renal Failure, Oral Changes, Dialysis, Renal Transplantation

Introduction

Chronic renal failure (CRF) represents an important worldwide health problem with a tendency for annual progression, and diabetic nephropathy is considered to be the most common cause of the end stage of renal disease. Patients, due to residual renal function and adaptation mechanisms of glomerular filtration rate, may pass through a long asymptomatic period. But, with progression of renal disease, through 5 stages and finally to irreversible bilateral renal destruction, comes to an increased occurrence of morbidities associated with this condition and rich symptomatology due to impact of many organs and organ systems. Under such circumstances there are also repercussions in the oral cavity.

Approximately 90% of all the affected patients have oral manifestations that originate from soft tissues, jaw bones and salivary glands. Which of the systemic complications and oral changes will appear in patients with CRF depends not only on the etiological factors, but also on the type of treatment they receive, ranging from usual measures of dietary restriction, various forms of dialysis, and finally to renal transplantation. Despite advantages of renal replacement therapy, some oral abnormalities, as uremic smell, xerostomia, unpleasant taste and mucosal pain are irreversible and further persist regardless the adequate medical treatment.

The aims of this study were to make comparative evaluation of objective oral clinical findings and subjective oral symptoms in patients with CRF undergoing various treatments, and to find possible link between subjective symptoms and objective clinical findings.
Material and Methods

A total of 90 patients with CRF were included in this study. Selection of the patients was made at the University Nephrology Department in Skopje, and the eponymous haemodialysis center. Complete case histories and clinical examinations were performed at the University Department of Oral Medicine and Periodontology; laboratory investigations were done at the Institute for Microbiology, Medical Faculty in Skopje.

All participants included in this study were divided into 3 groups:
- The first group (group A) consisted of 30 patients with CRF and serum creatinine level less than 120 μmol/L;
- The second group (group B) consisted of 30 patients with CRF undergoing haemodialysis;
- The third group (group C) consisted of 30 patients with renal transplants.

All patients regardless to the group were from both genders, aged 18 to 65 years. In patients undergoing haemodialysis, the treatment was performed 3 times a week, lasting 3 hours per session. Patients with renal transplants, in their main therapy, were receiving Cyclosporine in a daily dosage of 125 mg (Neoral; 6 - 8mg/kg).

All subjects were informed about the procedure and agreed to participate in the study. For all patients included in the study were noted information about their oral health status 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. Through anamnestic data, the most common subjective oral symptoms and signs were recorded, as follows: uremic foetor, unpleasant taste, thirst, xerostomia and burning tongue. Uremic foetor was recorded as a urine-smell breath, and unpleasant taste due to loss of sensation of different tastes in food. Diagnosis of xerostomia was made when the patients reported dry mouth and during oral inspection dental instrument was sticking to the oral mucosa.

Oral lesions were registered according to acknowledged clinical diagnostic criteria. Dry and fissured lips were recorded when smaller or larger squamous formations on mildly erythematous vermillion surface were observed. Coated tongue was recorded as dirty white plaque formations on the dorsal surface, which could be easily removed, and also elongated filiform papillae were present. Uremic stomatitis was registered as a form of irregular mildly erythematous areas covered with greyish white pseudo-membranes localized on lateral borders and dorsum of the tongue or buccal mucosa, accompanied with painful sensations. Gingival enlargement was observed in the region of marginal gingiva and interdental papilla.

Detection of Candida Albicans

Material from oral mucosa was taken with swab stick by rotational movements from each patient. It was placed in a sterile tube and within 2 hours distributed to the Institute of Microbiology where it was cultivated on Sabouraud agar or selective agar surface. The sample was kept in agar for 48-72 hours prior to determination of the results.

Statistical Analysis

The obtained data were presented as percentages of total and were statistically processed using the program Statistica 7.1. Kruskall-Wallis-test was used to assess the significance of differences in distribution of oral lesions and symptoms among the studied groups. The degree of difference between 2 groups was assessed using Mann-Whitney U-test. Intra-group association between oral symptoms and oral lesions was examined with Wilcoxon Signed Rank test.

Results

The results are presented in tables 1-3.
Table 2. Oral lesions in study groups

<table>
<thead>
<tr>
<th>Oral lesion</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>p(a:b)</th>
<th>p(a:c)</th>
<th>p(b:c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pale oral mucosa</td>
<td>16</td>
<td>25</td>
<td>23</td>
<td>0.013</td>
<td>0.060</td>
<td>0.522</td>
</tr>
<tr>
<td>Dry fissured lips</td>
<td>22</td>
<td>27</td>
<td>8</td>
<td>0.098</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>Coated tongue</td>
<td>23</td>
<td>30</td>
<td>24</td>
<td>0.005</td>
<td>0.756</td>
<td>0.010</td>
</tr>
<tr>
<td>Candidiasis</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0.013</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Petechiae or ecchymoses</td>
<td>0</td>
<td>27</td>
<td>4</td>
<td>0.000</td>
<td>0.040</td>
<td>0.000</td>
</tr>
<tr>
<td>Uremic stomatitis</td>
<td>0</td>
<td>4</td>
<td>4</td>
<td>0.040</td>
<td>0.040</td>
<td>1.000</td>
</tr>
<tr>
<td>Erythema</td>
<td>23</td>
<td>20</td>
<td>12</td>
<td>0.394</td>
<td>0.004</td>
<td>0.040</td>
</tr>
<tr>
<td>Angular cheilitis</td>
<td>14</td>
<td>19</td>
<td>6</td>
<td>0.198</td>
<td>0.030</td>
<td>0.001</td>
</tr>
<tr>
<td>Gingival enlargement</td>
<td>0</td>
<td>0</td>
<td>14</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Intra-group associations between oral symptoms, signs and oral lesions in all study groups

<table>
<thead>
<tr>
<th>Groups</th>
<th>Symptoms, signs</th>
<th>Oral lesions</th>
<th>Wilcoxon Signed Ranks Test</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>Uremic fetor</td>
<td>Uremic stomatitis</td>
<td>Z=1.897</td>
<td>0.058</td>
</tr>
<tr>
<td></td>
<td>Unpleasant taste</td>
<td>Saburral tongue</td>
<td>Z=3.873</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Thirst</td>
<td>Dry fissured lips</td>
<td>Z=1.732</td>
<td>0.083</td>
</tr>
<tr>
<td></td>
<td>Xerostomia</td>
<td>Saburral tongue</td>
<td>Z=2.714</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td>Xerostomia</td>
<td>Angular cheilitis</td>
<td>Z=1.871</td>
<td>0.061</td>
</tr>
<tr>
<td></td>
<td>Xerostomia</td>
<td>Erythema</td>
<td>Z=2.714</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td>Burning tongue</td>
<td>Uremic stomatitis</td>
<td>Z=0.000</td>
<td>1.000</td>
</tr>
<tr>
<td>Group B</td>
<td>Uremic fetor</td>
<td>Uremic stomatitis</td>
<td>Z=3.606</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Unpleasant taste</td>
<td>Saburral tongue</td>
<td>Z=4.472</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Thirst</td>
<td>Dry fissured lips</td>
<td>Z=2.01</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>Xerostomia</td>
<td>Saburral tongue</td>
<td>Z=3.276</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Xerostomia</td>
<td>Angular cheilitis</td>
<td>Z=0.180</td>
<td>0.857</td>
</tr>
<tr>
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<td>Xerostomia</td>
<td>Erythema</td>
<td>Z=0.474</td>
<td>0.635</td>
</tr>
<tr>
<td></td>
<td>Burning tongue</td>
<td>Uremic stomatitis</td>
<td>Z=1.667</td>
<td>0.096</td>
</tr>
<tr>
<td>Group C</td>
<td>Uremic fetor</td>
<td>Uremic stomatitis</td>
<td>Z=2.828</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>Unpleasant taste</td>
<td>Saburral tongue</td>
<td>Z=3.128</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>Thirst</td>
<td>Dry fissured lips</td>
<td>Z=2.500</td>
<td>0.012</td>
</tr>
<tr>
<td></td>
<td>Xerostomia</td>
<td>Saburral tongue</td>
<td>Z=2.558</td>
<td>0.011</td>
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<tr>
<td></td>
<td>Xerostomia</td>
<td>Angular cheilitis</td>
<td>Z=2.449</td>
<td>0.014</td>
</tr>
<tr>
<td></td>
<td>Xerostomia</td>
<td>Erythema</td>
<td>Z=0.000</td>
<td>1.000</td>
</tr>
</tbody>
</table>
Statistically significant differences were found in the distribution of uremic foetor (Z=2.337, p=0.019) and subjective feeling of burning tongue (Z=3.227, p=0.001) between patients with CRF in pre-dialysis stadium and patients with CRF undergoing haemodialysis. There was no statistically significant difference in the prevalence of xerostomia (Z=2.053, p=0.040) and burning tongue (Z=2.316, p=0.021) between haemodialysis patients and renal transplant patients. Statistically significant difference has not been found in the prevalence of unpleasant taste and subjective feeling of thirst among the different groups of patients (Tabs. 1 and 3).

We observed statistically significant difference in the prevalence of pale mucosa (Z=2.477, p=0.013), coated tongue (Z=2.791, p=0.005), petechiae and/or ecchymoses (Z=6.948, p=0.000) and uremic stomatitis (Z=2.053, p=0.040) between pre-dialysis patients and haemodialysis patients (Tabs. 2 and 3). Between pre-dialysis patients and renal transplant patients we observed statistically significant difference in the prevalence of dry, fissured lips (Z=3.585, p=0.000), and the presence of petechiae and/or ecchymoses (Z=2.053, p=0.040), uremic stomatitis (Z=2.053, p=0.040), erythema (Z=2.856, p=0.004) and angular cheilitis (Z=2.173, p=0.030). Between haemodialysis patients and renal transplant patients we observed statistically significant difference in the prevalence of xerostomia (Z=4.934, p=0.000), coated tongue (Z=2.560, r=0.010), presence of petechiae and/or ecchymoses (Z=5.892, p=0.000), erythema (Z=2.053, r=0.040) and angular cheilitis (Z=3.376, p=0.001).

The Kruskal-Wallis test showed statistically significant difference in the prevalence of gingival enlargement and candidiasis (x²=11.09; df=2; p<0.01) among all the studied groups.

In the group of pre-dialysis patients, we found a significant association between following subjective and objective clinical oral findings: unpleasant taste and coated tongue, xerostomia and coated tongue, xerostomia and erythema. In the group of haemodialysis patients, we found a significant association between: uremic foetor and uremic stomatitis, unpleasant taste and coated tongue, thirst and dry fissured lips, xerostomia and coated tongue. In the group of renal transplant patients, we found a significant association between: uremic foetor and uremic stomatitis, unpleasant taste and coated tongue, thirst and dry fissured lips, xerostomia and coated tongue, xerostomia and angular cheilitis.

**Discussion**

To our knowledge, this is the first study in FYROM in this field - investigating oral manifestations in CRF patients undergoing different treatments. Based on the findings from this study, as we expected, the highest prevalence of oral symptoms and lesions was recorded in haemodialysis patients, and the lowest percentage was recorded in renal transplant patients. We believe that this is due to the fact that haemodialysis patients are not very suitable for routine dental treatment, their dependence on dialysis centres, and their lack of motivation and less priority to maintain oral health due to the severity of their primary disease. On the other hand, transplant patients are aware that maintaining oral health at high level is necessary to prevent oral infection, which can jeopardize the success of the transplantation, but nevertheless, certain oral manifestations occur as a side effect of post-transplantation immunosuppressive therapy.

In our study, most frequent oral symptom among patients from each group was subjective feeling of thirst, symptom present in 65 out of 90 patients (72.22%). Xerostomia and uremic foetor followed, which is consistent with findings in other studies. We think that thirst in haemodialysis patients appears as a result from the fluid restriction implemented in order to prevent fluid overload between dialysis sessions, and as a consequence of the present hyposalivation. We believe that thirst in renal transplant patients is a complex phenomenon, predominantly due to a synergistic side effect of immunosuppressive and corticosteroid therapy that these patients receive. After thirst, as a second most frequent oral symptom in all the patients in our study was xerostomia, present in 54% OUT of 90 patients. Some higher rates have recorded Junn et al in their study, where xerostomia was present among 68.9% of 90 haemodialysis patients. According to Hamid et al, xerostomia is common among patients with CRF. Patients included in this study, apart from their main treatment, also received ACE-inhibitors, antidepressants and sedatives. This additional medical treatment worsened the symptoms, which is probably the most responsible factor for xerostomia as a side-effect. In our study, we found an association between xerostomia and coated tongue in all the patients, and also association between xerostomia and erythema in patients of group A, as well as xerostomia and angular cheilitis in patients of group C. The latter association was expected because angular cheilitis occurs in persons with present oral dryness, individuals under immunosuppressive therapy, or among dehydrated patients. However, the number of registered cases with angular cheilitis among renal transplant patients was significantly lower compared to pre-dialysis and haemodialysis patients.

In a way, xerostomia is an additional cause for the uremic bad foetor and unpleasant taste, which were more prevalent in groups A and B. Postorino et al registered dry mouth associated with unpleasant metallic taste in patients with terminal stage of CRF who had diabetes. Similarly, our findings showed almost equal distribution of unpleasant taste among all 3 groups, which supports the
opinion that in all uremic patients, regardless the type of treatment, there is a distortion of taste perception.7

Low oral hygiene status and dental plaque accumulation due to de-motivation in patients who are in this condition are additional factors that jeopardize the obtained clinical finding. In our study, we noted association between unpleasant taste and the appearance of coated tongue among each of the investigated groups. According to our study, the coated tongue was the most common oral change of chronic renal patients. Similar results were presented in previous reports.5,6,17. Coated tongue in our study was present in all haemodialysis patients (group B). Retention of residues of food, desquamated epithelial cells and bacterial accumulation due to the filiform papillae enlargement, aggravated maintenance of oral hygiene and decreased amount of saliva, being all the main reasons for the appearance of this common oral manifestation.25. In this context, quite logical is the obtained strong association between the coated tongue and xerostomia among all the examined patients with CRF.

The uremic foetor was the third most frequent oral symptom among the CRF patients, present in highest percentage in patients of the group B, and with the least prevalence in patients of the group A. The uremic foetor found in 56.66% patients on haemodialysis is similar to that reported by Kao et al15 and Estela De La Rosa et al5. The uremic foetor in patients with CRF is considered to be a consequence of the high concentration of urea in saliva and its posterior transformation into ammonium.5,26,27. Investigating the intra-group association between oral symptoms and oral changes, we have found association between uremic foetor and uremic stomatitis among haemodialysis patients and renal transplant patients. No association was found between burning tongue and any of the oral manifestations, which is in agreement with findings in the study of De La Rosa et al6. Predominant reasons for the appearance of burning tongue are dried oral mucosa, xerostomia due to several reasons, the presence of candidiasis, prolonged clearance of medications, as well as vitamin deficit. This oral symptom was not detected among patients with CRF in pre-dialysis phase.

Frequent observation among all participants was pale mucosa, present in 64 of a total of 90 CRF patients, and its prevalence in group B was 90%. The appearance of pale mucosa in renal patients we explain by anaemia, which as a complication appearing in the early stadium of chronic renal disease and progressing with further loss of renal function.

We registered high prevalence of dry fissured lips, which were recorded among 27 patients of group B (90%), 22 patients from group A and only in 8 patients of group C. De la Rosa et al6 reported the presence of dry mouth in 28.3% patients with terminal renal disease and absence of any association with the other oral symptoms and changes. In contrast, in our study, we have found strong association between dry fissured lips and thirst in dialysis and renal transplant patients.

Despite the fact that candidiasis is presented as a common oral manifestation in patients with renal transplants, in which usually occurs in the first few months of post-transplantation period, Candida albicans was determined in only 3 patients on haemodialysis. According to the data in the literature,9,32, the prevalence of oral candidiasis in patients with CRF who are on haemodialysis ranges from 5.7% to 37%. We consider that in patients on haemodialysis, who are immunocompromised due to suppression of cellular-induced immunity and dysfunction of granulocytes caused by persisting uraemia,22,24,27, their poor oral hygiene, xerostomia and diabetes as most often etiological factor for the CRF, make this group of patients high susceptible for oral infections. Therefore, the presence of oral candidiasis is not surprising, as Candida albicans presents an integral part of the normal oral microflora, and so represents endogenous infection. The absence of oral candidiasis among transplant patients in this study could be explained by the fact that most of the patients were young, with optimal level of oral hygiene, and the rest of the patients were old, with medical history of several transplant graft rejections and occurrences of oral candidiasis in the past.

Gingival enlargement, as one of the most known oral manifestation among transplanted patients, whose prevalence according to data from different reports18,30 ranges from 22% to 81%, in our research was detected in 14 (46.66%) renal transplant patients from group C. The undisputed fact is that cyclosporine treatment leads to this kind of oral alteration, but it raises the question of whether the dose of cyclosporine or duration of the therapy has more important role in the development of gingival enlargement. Regarding this issue, opinions are very controversial.3,11,16,23. Still, it has generally been accepted that pathogenesis of cyclosporine-induced gingival enlargement represents complex mechanism, which includes number of cellular, local and hereditary factors. We suppose that this clinical finding can additionally be exacerbated by antihypertensive drugs.

From the conducted researches, we were not able to find an association between the gingival enlargement and any of the noted oral symptoms, but we found an association with uremic stomatitis, or precisely, among 4 out of 14 total transplant patients with gingival enlargement, simultaneously was evidenced the presence of uremic stomatitis as well. The uremic stomatitis was also evidenced among 4 patients undergoing haemodialysis and not even in 1 case among CRF patients in pre-dialysis phase. The uremic stomatitis was diagnosed as painful erythematous area on the buccal and labial mucosa, covered with greyish exudates. Leão et al19 and Ross and Salisbury28 came out to the same
result in their researches. The results of the obtained statistical analysis showed association between uremic stomatitis and uremic foetor, which was expected due to their identical causal factor - rapid increase in serum and salivary urea concentration.

Erythematous appearances on the oral mucosa surface had highest prevalence among patients from group A, at whom we discovered a strong association between erythematous areas and oral dryness. Petechial bleeding in oral mucosa represents relatively common oral clinical finding in patients with CRF. In our study, this clinical finding was detected in 90% of patients on haemodialysis treatment. In contrast, Kho et al. inform for 12.2% and De la Rosa et al. for 15.2% prevalence of petechiae in patients on haemodialysis. We suppose that this clinical finding refers to the impaired platelet aggregation as a consequence of the uremic syndrome and accumulation of inhibitory factors in blood that cannot be removed with the process of dialysis. Heparin and other anticoagulants are additional causal factors. The petechiae and ecchymoses in transplant patients have been reported as a secondary consequence of the side-effects of immunosuppressive therapy.

Conclusion

The stadium and consequently severity of CRF, as well as the type of treatment, have influence on the severity of oral clinical finding in patients with CRF. Patients with CRF who were on the treatment with haemodialysis had higher prevalence of oral manifestations compared with CRF patients in predialysis phase and renal transplant patients. Coated tongue, thirst, pale oral mucosa and dry fissured lips were the most frequent oral symptoms and changes among all CRF patients, independently to which group they have belonged.

Monitoring of the patients with CRF, local preventive and curative oral treatment, as well as communication between nephrologists and dentists, are just a part of the measures for maintaining and improvement of oral health among patients with CRF.

References


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