ORAL CHANGES IN PATIENTS WITH CHRONIC RENAL FAILURE
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ABSTRACT
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 chronic renal failure divided into three groups: patients with CRF undergoing hemodialysis, patients with CRF without hemodialysis and serum creatinine <120μmol / L and patients with renal transplantation. Swab for Candida Albicans was taken from the 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 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 in which group they have belonged. Significant association was found between xerostomia and coated tongue and between unpleasant taste and coated tongue in all studied patients. Conclusion: The stadium and consequently severity of chronic renal disease as well as the type of treatment have influence on the severity of the oral clinical finding.

Key words: chronic renal failure, oral changes, dialysis, renal transplantation

INTRODUCTION
Chronic renal disease represents an important worldwide health problem with a tendency for annual progression (9), and diabetic nephropathy is considered for the most common cause of end stage of renal disease (ESRD). The 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 affection of many organs and organ systems. Under such circumstances there are also repercussions in the oral cavity.

Approximately 90 % of all affected patients (28) have oral manifestations that originate from soft tissues, jaw bones and salivary glands. Witch of the systemic complications and oral changes will appear in patients with chronic renal failure depends not only on the etiological factors , but also of the type of therapy that they receive, ranging from usual measures of dietary restriction (13,27), various forms of dialysis, and finally to renal transplantation (4,30). Despite
advantages of the renal replacement therapy, some oral abnormalities as uremic odor, xerostomia, unpleasant taste and mucosal pain are irreversible and further persist although the adequate medical treatment.

The aims of our study were to make comparative evaluation of objective oral clinical findings and subjective oral symptoms in patients with chronic renal failure undergoing various therapeutic treatments, and to find possible link between subjective symptoms and objective clinical findings.

MATERIAL AND METHODS

A total of 90 patients in whom chronic renal failure was diagnosed were included in this study. Selection of the patients was made at the University Nephrology Department in Skopje, and the eponymous hemodialysis center. Complete anamnestic procedure and clinical examination were performed at the University Department of Oral Medicine and Periodontology, and laboratory investigations were implemented at the Institute for Microbiology, Medical Faculty in Skopje.

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

All patients regardless of which group belonged were from both sexes, aged 18 to 65 years. In patients undergoing hemodialysis, the treatment was performed three times a week in duration of three hours per session. Patients with renal transplantation 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 were recorded the most common subjective oral symptoms and signs as follows: uremic fetor, unpleasant taste, thirst, xerostomia and burning tongue.

Uremic fetor was recorded as a urine-odor breath, and unpleasant taste as 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 (2, 27).

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 which could be easily removed and also elongated filiform papillae were present. Uremic stomatitis was registered as a form of irregular easily erythematous areas covered with grayish white pseudomembranes 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 gingival and interdentally papilla.

Detection of Candida Albicans

From each patient using a swab stick with rotational movements was taken the material from oral mucosa, placed in a sterile tube within 2 hours was distributed to the Institute.
of Microbiology where it was cultivated on Sabouraud agar or selective agar surface. The sample was kept 48-72 hours until 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. We used Kruskall-Wallis-test to assess the significance of differences in distribution of oral lesions and symptoms among all studied groups. The degree of difference between two groups was assessed using Mann-Whitney U test. Intra-group association between oral symptoms and oral lesions was examined using Wilcoxon Signed Rank test.

RESULTS

Table 1. Oral symptoms and signs in study groups

<table>
<thead>
<tr>
<th>Oral symptoms and signs</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>Uremic fetor</td>
<td>8</td>
<td>17</td>
<td>9</td>
<td>0.019</td>
<td>0.576</td>
<td>0.072</td>
</tr>
<tr>
<td>Unpleasant taste</td>
<td>8</td>
<td>10</td>
<td>9</td>
<td>0.576</td>
<td>0.713</td>
<td>0.851</td>
</tr>
<tr>
<td>Thirst</td>
<td>23</td>
<td>24</td>
<td>18</td>
<td>0.756</td>
<td>0.227</td>
<td>0.132</td>
</tr>
<tr>
<td>Xerostomia</td>
<td>22</td>
<td>20</td>
<td>12</td>
<td>0.501</td>
<td>0.079</td>
<td>0.040</td>
</tr>
<tr>
<td>Burning tongue</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0.001</td>
<td>0.154</td>
<td>0.021</td>
</tr>
</tbody>
</table>

Statistically significant differences was found in the distribution of uremic fetor ($Z = 2.337$, $p = 0.019$) 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 hemodialysis.

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 hemodialysis patients and renal transplant patients.

Statistically significant difference has not been found in the prevalence of unpleasant taste ($X^2 = 0.322$, df = 2, $p = 0.851$) and subjective feeling of thirst ($X^2 = 2.680$, df = 2, $p = 0.262$) among the different groups of patients.

Table 2. Oral lesions in study groups

<table>
<thead>
<tr>
<th>Oral lesions</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>
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 hemodialysis patients.

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 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 hemodialysis patients and renal transplant patients we observed statistically significant difference in the prevalence of xerostomia ($Z = 4.934$, $p = 0.000$), coated tongue ($Z = 2.560$, $p = 0.010$), petechiae and/or ecchymoses ($Z = 5.892$, $p = 0.000$), erythema ($Z = 2.053$, $p = 0.040$) 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 ($x^2 = 11.09$; $df = 2$; $p < 0.01$) among all studied groups.

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

<table>
<thead>
<tr>
<th>Group A</th>
<th>Symptoms, signs</th>
<th>Oral lesions</th>
<th>Wilcoxon Signed Ranks Test</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uremic fetor</td>
<td>Uremic stomatitis</td>
<td>$Z=1.897$</td>
<td>0.058</td>
<td></td>
</tr>
<tr>
<td>Unpleasant taste</td>
<td>Saburral tongue</td>
<td>$Z=3.873$</td>
<td><strong>0.000</strong></td>
<td></td>
</tr>
<tr>
<td>Thirst</td>
<td>Dry fissured lips</td>
<td>$Z=1.732$</td>
<td>0.083</td>
<td></td>
</tr>
<tr>
<td>Xerostomia</td>
<td>Saburral tongue</td>
<td>$Z=2.714$</td>
<td><strong>0.007</strong></td>
<td></td>
</tr>
<tr>
<td>Xerostomia</td>
<td>Angular cheilitis</td>
<td>$Z=1.871$</td>
<td>0.061</td>
<td></td>
</tr>
<tr>
<td>Xerostomia</td>
<td>Erythema</td>
<td>$Z=2.714$</td>
<td><strong>0.007</strong></td>
<td></td>
</tr>
<tr>
<td>Burning tongue</td>
<td>Uremic stomatitis</td>
<td>$Z=0.000$</td>
<td>1.000</td>
<td></td>
</tr>
</tbody>
</table>

Group B

| Uremic fetor | Uremic stomatitis | $Z=3.606$ | **0.000** |
| Unpleasant taste | Saburral tongue | $Z=4.472$ | **0.000** |
| Thirst | Dry fissured lips | $Z=2.01$ | **0.005** |
| Xerostomia | Saburral tongue | $Z=3.276$ | **0.001** |
| Xerostomia | Angular cheilitis | $Z=0.180$ | 0.857 |
| Xerostomia | Erythema | $Z=0.474$ | 0.635 |
| Burning tongue | Uremic stomatitis | $Z=1.667$ | 0.096 |

Group C

| Uremic fetor | Uremic stomatitis | $Z=2.828$ | **0.005** |
| Unpleasant taste | Saburral tongue | $Z=3.128$ | **0.002** |
| Thirst | Dry fissured lips | $Z=2.500$ | **0.012** |
| Xerostomia | Saburral tongue | $Z=2.558$ | **0.011** |
| Xerostomia | Angular cheilitis | $Z=2.449$ | **0.014** |
| Xerostomia | Erythema | $Z=0.000$ | 1.000 |

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 hemodialysis patients we found a significant association between:
uremic fetor 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 fetor 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 Macedonia in this field, investigating oral manifestations in CRF patients undergoing different therapy. Based on the findings from this study as we expected the highest prevalence of oral symptoms and lesions was recorded in hemodialysis patients and the lowest percentage was recorded in renal transplant patients. We believe this result came out because hemodialysis patients are not very suitable for routine dental treatment, their dependence on dialysis centers and also because of their lack of motivation and less priority to maintain oral health contrary 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 infections 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 %). After thirst, followed xerostomia and uremic fetor, which is consistent with findings in other studies (5, 6, 14, 17, 21, 22) We think that thirst in hemodialysis patients appears as a result from the fluid restriction implemented in order to prevent fluid overload between dialysis sessions, and as a consequence of present hyposalivation. The reason for the presence of thirst in renal transplant patients we believe that has a complex nature and predominantly role plays the synergistic side effect of immunosuppressive and corticosteroid therapy that these patients receive. After thirst as second most frequent oral symptom in all renal patients in our study occur xerostomia, present in 54% out of 90 patients. Some higher rates has recorded Junn-Ming-Sung (14) in his study where xerostomia was present among 68, 9% of 90 hemodialysis patients. According to Hamid (10) xerostomia is common among patients with chronic renal failure. The patients included in this study despite their main therapy also receive ACE-inhibitors, antidepressants and sedatives. This additional medical therapy worsens the situation and we believe that is most responsible for the present oral dryness (xerostomia) as a side effect. In our study we found an association between xerostomia and coated tongue in all renal patients, association between xerostomia and erythem in patients of group A, as well as association between xerostomia and angular cheilitis in patients of group C. This 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 hemodialysis patients. In a way xerostomia is an additional cause for the uremic bad odor and unpleasant taste which is more prevalent in groups A and B. Postorino (29) registered a dry mouth, which was associated with unpleasant metallic taste in patients with terminal stage of chronic renal failure, who had diabetes. Approximately, our findings for almost equal distribution of unpleasant taste among all three groups, were quite expected
and supports the opinion that in all uremic patients regardless of whether they are on hemodialysis or other type of therapy, comes to distortion of taste perception. (7) Low oral hygiene status, dental plaque accumulation due to demotivation from the patients who are in this condition are additional factors which jeopardize the obtained clinical finding. In our study we have 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 documented and other authors in previous reports (5, 6, 17). Coated tongue in our study was present in all hemodialysis patients of 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 are the main reasons for the appearance of this common oral manifestation (33). In this context, quite logical is the obtained strong association between the coated tongue and xerostomia among all examined patients with CRF.

The uremic fetor was third most frequent oral symptom among the chronic renal patients, present in highest percentage in patients of group B (17 patients, 56.66%) and with the least prevalence in patients of group A (8 patients, 26.66%). The 56, 66% uremic fetor found in patients on hemodialysis, is similar to that reported by Kao et al. (50%) (15) and Estela De La Rosa (48%) (5). The uremic fetor in patients with CRF is considered that appears as a consequence of the high concentration of urea in saliva and its posterior transformation into ammonium. (5, 27, 28) Investigating the intra-group association between oral symptoms and oral changes we have found association between uremic fetor and uremic stomatitis among hemodialysis patients and renal transplant patients.

No association was found between burning tongue and any of the oral manifestations, which is in agreement with the findings in the study of Estela De La Rosa (5). Predominant reasons for the appearance of burning tongue are dried oral mucosa, xerostomia due to most various etiologies, 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 chronic renal patients, and its prevalence in group B was 90%. The appearance of pale mucosa in renal patients, we explain by anemia, which as complication of chronic renal disease is appearing in the early stadium and progresses with further loss of the renal function.

We registered high prevalence of dry fissured lips which were recorded among 27 patients (90%) of group B, 22 patients from group A and only in 8 patients of group C. De la Rosa et al. (5) reported 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 common oral manifestations in patients with renal transplants in which usually occurs in the first few months of post-transplantation period, out of all study subjects only among 3 patients on hemodialysis was determined positive Candida Albicans findings. According to the data in the literature (8, 33) prevalence of oral candidiasis in patients with CRF who are on treatment with hemodialysis ranges from 5.7% to 37%. We consider that the patients
on hemodialysis who are immunocompromised due to suppression of cellular-induced immunity and dysfunction of granulocytes caused by persisting uremia (23, 28), their poor oral hygiene, xerostomia and diabetes as most often etiological factor for CRF, make this group of patients high susceptible for oral infections. Therefore, should not be surprising the presence of infection by Candida Albicans, which present an integral part of the normal oral microflora, and in this case it is endogenous infection.

The absence of oral candidiasis among transplant patients in this study we can explain with the fact that most of the patients were young with optimal level of oral hygiene and the rest of the patients were old aged with medical history of several transplant graft rejection 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 reports (18, 31) 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 the cyclosporine 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, 24). Still, generally has been accepted the fact that pathogenesis of cyclosporine-induced gingival enlargement represents complex mechanism which includes number of cellular, local and hereditary factors. We suppose that antihypertensive drugs can also exacerbate this clinical finding.

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 \((r = 0.419, p < 0.01)\), or among 4 out of 14 total transplant patients with gingival enlargement simultaneously was evidenced presence of uremic stomatitis as well. The uremic stomatitis was also evidenced among four patients undergoing hemodialysis, and not even one case with uremic stomatitis was registered among CRF patients in pre-dialysis phase. The uremic stomatitis was diagnosed as painful erythematous area on the buccal and labial mucosa and covered with grayish exudates.

Leao (19) and Ross (29) came out to the same realization in their researches. The results of obtained statistical analysis showed association between uremic stomatitis and uremic fetor, which was totally expected due their identical causal factor, rapidly increased serum and salivary urea concentration(1). Erythematous appearances on the oral mucosa surface had highest prevalence among the patients from group A at whom we discovered that there is a strong association between erythematous areas and oral dryness.

Petechia bleeding in oral mucosa represents relatively common oral clinical finding seen in patients with chronic renal failure. In our study this clinical finding was detected in 90% of patients on hemodialysis treatment. In contrast, Kno (17) informs for 12.2% and De la Rosa (5) for 15.2% prevalence of petechiae in patients on hemodialysis. We suppose that this clinical finding referees to the impaired platelet aggregation as a consequence of the uremic syndrome and accumulation of inhibitory factors in the blood that cannot be removed with the process of dialysis. Heparin and other anticoagulants are additional causal factors. The petechiae and ecchymosis in transplant patients have been reported as a secondary consequence of the unwanted effects of immunosuppressive therapy (32).
CONCLUSIONS

The stadium and consequently severity of chronic renal disease as well as the type of treatment have influence on the severity of the oral clinical finding in patients with CRF. Patients with CRF who were on treatment with hemodialysis had higher prevalence of oral manifestations compared with the patients with CRF in pre-dialysis 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 in which group they have belonged.

Monitoring of the patients with CRF, local preventive and curative oral treatment as well as collaboration between nephrologists and dentists are just part of the measures for maintaining and improvement of the oral health among patients with chronic renal failure

REFERENCES


22. Nandan RK, Sivapathanudham B, Sivakumar G. Oral manifestations and analysis of salivary and blood urea levels of patients undergoing haemodialysis and kidney transplant.


