

Oral findings, salivary creatinine and urea levels in CKD patients on hemodialysis and on conservative treatment.

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Abstract

Introduction: Chronic kidney disease is a gradual loss of kidney function with diabetes and hypertension as the leading cause. It is one of the systemic diseases that can affect the contents of salivary secretion. Saliva can indicate creatinine and urea levels in patients with chronic kidney disease which are the parameters that generally measured in blood samples.

Aims: This study aimed to determine oral findings and to assess salivary creatinine and urea levels in chronic kidney disease patients on hemodialysis and those on conservative treatment.

Materials and methods:

A total of 90 subjects were included in this study, divided into three groups: 30 chronic kidney disease patients on hemodialysis; 30 chronic kidney disease patients on conservative treatment and 30 healthy participants. Oral examination was done for each participant with the oral manifestations were recorded in the case sheet. Creatinine was estimated in saliva samples by colorimetric method. Salivary urea level was measured by Roche - Cobas C 111 analyzer automatically.

Results:

Dry mouth, uremic fetor, taste change were the most common oral findings in chronic kidney disease patients. Creatinine and urea level was higher in both patients groups compared to control subjects, while there was no significant difference between chronic kidney disease patients on hemodialysis and those on conservative treatment regarding salivary creatinine and urea level.

Conclusions:

Salivary creatinine and salivary urea were higher in both chronic kidney disease patients on hemodialysis and on conservative treatment compared to control subjects.

Key words: Chronic kidney disease, hemodialysis, salivary creatinine and salivary urea.

INTRODUCTION

Chronic kidney disease (CKD) is a progressive reduction in kidney function (1), with the diabetes and hypertension are the most common related cause (2).

Chronic kidney disease is classified into five stages according to the level of proteinuria and kidney function which is measured by the estimated glomerular filtration rate (eGFR) which is derived from age, gender, race and serum creatinine concentration (3). Patients develop End-Stage Renal Disease (ESRD) once bilateral deterioration of nephrons pass the point of compensation therefore; dialysis therapy and renal transplantation are life-saving procedures in these patients (4).

In hemodialysis, urea and other low molecular weight substances diffuse during interchange from the patient's blood across an extra-corporal filtering/dialysis membrane into an electrolyte and pH balanced dialysis solution (5). The frequency and duration of dialysis are related to residual kidney function, protein intake, body size and tolerance to fluid elimination. Typically, patient undergoes hemodialysis three times per week, with each treatment session about three to four hours on standard dialysis units and slightly less time on high efficiency or high-flux dialysis units (6).

In studies of patients with kidney disease, up to 90% were found to have oral findings of uremia. Some of the presenting signs in renal patients were an ammonia-like taste and smell, gingivitis, stomatitis, reduced salivary flow, xerostomia, and parotitis (6).

Diminished erythropoietin and the resultant anemia lead to paleness of the oral mucosa. Impairment of platelet function is occur during uremia (7). This situation combined with the heparin use and other anticoagulants in hemodialysis, lead patients to become prone to ecchymosis, petechiae, and hemorrhages in the oral cavity (8).

Saliva is considered as a filtrate of the blood where different molecules pass through transcellular or paracellular routes (passive intracellular diffusion and active transport or extracellular ultrafiltration respectively) into saliva. As a result, saliva is equivalent to serum, therefore reflecting the physiological state of the body (9).

Numerous systemic diseases have been reported to cause marked and identifiable alterations in salivary secretion. CKD is one of these systemic diseases that can affect the salivary composition. Saliva can indicate creatinine and urea levels in patients with CKD which are the parameters generally measured in blood samples. Measurement of salivary creatinine and urea in patients with CKD offers several advantages that have been attributed to the saliva use as a diagnostic fluid (10).

MATERIAL AND METHODS

A total of ninety (90) subjects were included in this study, divided into three groups: thirty patients with CKD on hemodialysis for at least 6 months ago; thirty patients with CKD on conservative treatment and thirty healthy control participants. This study was done at Al-kindey teaching hospital in Al-kindey dialysis center in Baghdad during the period from December 2017 to the end of February 2018.

Patients were excluded from this study: Patients under chemotherapy or/and radiotherapy, patients undergo hemodialysis due to acute kidney failure or accident and hepatitis patients.

For all participants in this study, a case sheet was fulfilled including patients demography, risk factors, family history, medical history, history of present illness, investigations (serum creatinine and urea), oral manifestations and salivary parameters (salivary flow rate and PH).

Oral examination was done for each participant with the oral manifestations were recorded in the case sheet.

After oral examination, saliva was collected from all individuals under the same conditions and each participant was instructed to rinse and wash his/her mouth with distilled water before saliva collection. Saliva was collected before meal or at least one hour after meal by spitting method for about 5-minutes. Sampling sessions limited to the hours between 9:00 and 11:00 AM to minimize the effect of diurnal variations.

The samples was identified by a code number during the time of sample collection and processing. After collection of saliva samples, they were placed in a small cooler box to stop growth of bacteria and then, centrifuged at 3000 rpm for 10 minutes (11). The clear supernatant was taken and stored at -20°C until the time of analysis.

Creatinine was estimated in saliva samples by colorimetric method using randox creatinine manual kit and biolabo - kenza max biochemistry analyzer. Salivary urea was measured by Roche - Cobas C 111 analyzer automatically by using cobas ureal kit.

Statistical analysis:

Statistical analysis was performed with SPSS (Statistical Package for Social Sciences; Version 21). Descriptive statistical analysis, contingency coefficient, student T-test, Analysis of Variance (ANOVA), Post-hoc (LSD and Dunnett T3) tests and Person Correlation Coefficient (r) were used in this study. *P* < 0.05 significant; *P* < 0.01 highly significant; *P* > 0.05 non-significant.

RESULTS:

Demography

The age range at first presentation was 25-75 years with an overall mean age of 49.6 years. Forty six of them were males with a mean age of 47.8 and 44 of them were females with a mean age of 51.4. Thirty patients were with CKD on hemodialysis with an age range of 37-75 years and a mean age of 55.3. Seventeen of them were males and 13 were females, other thirty patients were with CKD on conservative treatment with an age range of 25-75 years and a mean of 49.3. Sixteen of them were males and 14 were females and thirty healthy subjects with an age range of 27-63 years and a mean of 44.2. Thirteen of them were males and 17 were females.

A statistical analysis using contingency coefficient revealed that there was no significant difference in relation to age (*P*=0.06) or gender (*P*=0.056) among study groups.

Regarding occupation, thirty one (34.4%) of the participants were retired followed by 24 (26.67%) were unemployed then 22 (24.4%) were workers and 13 (14.4%) were officers.

In CKD patients on hemodialysis, the majority were unemployed 13 (43.3%) followed by 9 (30%) were retired, 4 (13.3%) were workers and 4 (13.3%) were officers. In those on conservative treatment most of them were retired 14 (46.6%) followed by 10 (33.3%) were workers, 3 (10%) were unemployed and 3 (10%) were officers.

In control group, 8 (26.6%) were retired, 8 (26.6%) were unemployed, 8 (26.6%) were workers and 6 (20%) were officers.

A statistical analysis using contingency coefficient showed that there was no significant difference among study groups regarding occupation (*P* = 0.06).

Considering marital status, married participants were the most common (67) followed by single (16), widowed (5) and divorced (2).

In CKD patients on hemodialysis, the majority were married 27 (90%) and 3 (10%) were single. In those on conservative treatment, 19 (63.3%) were married followed by 6 (20%) were single, 3 (10%) were widowed and 2(6.6%) were divorced.

In control group, 21 (70) were married followed 7 (23.3%) were single and 2 (6.6%) were widowed.

Also, there was no significant difference among study groups considering marital status (*P* = 0.21).

Oral manifestations:

Figure (1) and figure (2) showed the oral manifestations in CKD patients on hemodialysis and those on conservative treatments.

In CKD on hemodialysis, uremic fetor was seen in 15 (50%) followed by dry mouth in 14 (46.6%), taste change in 13 (43.3%), Pale oral mucosa in 12 (40%), aphthus ulceration in 7 (23.3%), gingival enlargement in 4 (13.3%), burning sensation in 2 (6.6%) and angular cheilitis in 1 (3.3%) of patients.

In those on conservative treatment, taste change was seen in 14 (46.6%) followed by dry mouth in 11 (36.6%), uremic fetor in 10 (33.3%), Pale oral mucosa in 6 (20%), aphthus ulceration in 5

(16.6%), gingival enlargement in 5 (16.6%), burning sensation in 3 (10%) and angular cheilitis in 1 (3.3%) of patients.

No significant differences were found in oral manifestations between CKD patients on hemodialysis and CKD patients with conservative treatment; tables (1).

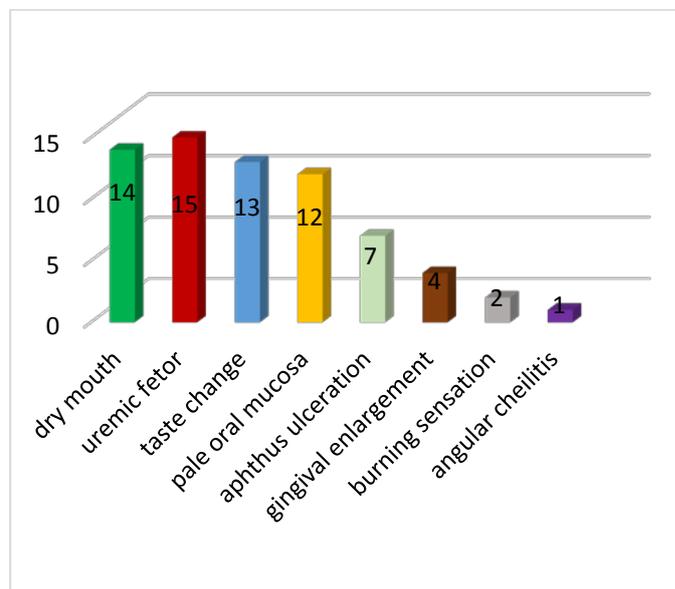


Figure (1): Oral manifestations in CKD patients on hemodialysis.

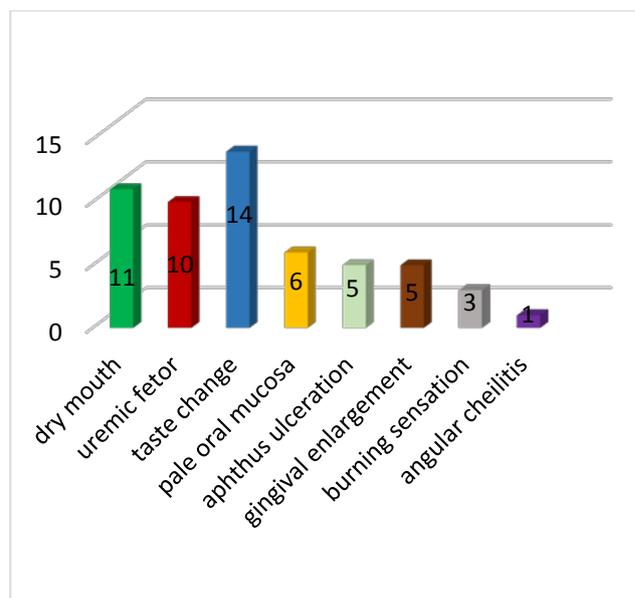


Figure (2): Oral manifestations in CKD patients with conservative treatment.

Laboratory findings:

Salivary and serum creatinine

Figure (3) shows the mean serum and salivary creatinine in CKD patients on hemodialysis and on conservative treatment with salivary creatinine in control group.

There was a significant difference in salivary creatinine of CKD patients on hemodialysis, those on conservative treatment and control group using ANOVA test; table (2).

Using post hoc (LSD) test, there was a significant increase in salivary creatinine level in both CKD patients on hemodialysis and those on conservative treatment compared to control group (*p*= 0.00, *p*= 0.00). While, no significant salivary creatinine difference was found between patients on hemodialysis and those on conservative treatment (*p*=0.90).

Using T test, no significant difference in serum creatinine of CKD patients on hemodialysis and those with conservative treatment (p= 0.06).

3.3.2. Salivary and blood urea:

Figure (4) shows the mean blood and salivary urea in CKD patients on hemodialysis and on conservative treatment with salivary urea in control group.

A statistical analysis using ANOVA test showed that there was a significant difference among salivary urea of CKD patients on hemodialysis, those on conservative treatment and control group; table (3).

Using a post hoc (Dunnett T3) test, there was a significant increase in salivary urea level in both CKD patients on hemodialysis and those on conservative treatment compared to

control group (P = 0.00, P = 0.00). While, there was no significant salivary urea difference was seen between patients on hemodialysis and those on conservative treatment (P = 0.35). Using T-test, there was no significant difference between CKD on hemodialysis and those on conservative treatment regarding blood urea levels (P = 0.94).

Correlation coefficient

There was a significant positive correlation between salivary creatinine and serum creatinine in both CKD patients on hemodialysis (r= 0.770, p= 0.00) and those on conservative treatment (r= 0.932, p= 0.00); Also, a significant positive correlation between salivary urea and blood urea in CKD patients on hemodialysis (r= 0.860. p= 0.00) and those on conservative treatment (r= 0.858, p= 0.00); table (4).

Table (1): Oral manifestations in CKD patients on hemodialysis and those on conservative treatment with contingency coefficient.

		Group		C.C	P value
		CKD (HD)	CKD		
Dry mouth	No. (%)	14 (46.6%)	11 (36.6%)	0.101	0.432 NS
Uremic fetor	No. (%)	15 (50%)	10 (33.3%)	0.16	0.190 NS
Taste change	No. (%)	13 (43.3%)	14 (46.6%)	0.03	0.795 NS
Pale oral mucosa	No. (%)	12 (40%)	6 (20%)	0.21	0.091 NS
Aphthous ulceration	No. (%)	7 (23.3%)	5 (16.6%)	0.08	0.519 NS
Gingival enlargement	No. (%)	4 (13.3%)	5 (16.6%)	0.04	0.718 NS
Burning sensation	No. (%)	2 (6.6%)	3 (10%)	0.060	0.640 NS
Angular cheilitis	No. (%)	1 (3.3%)	1 (3.3%)	0.00	1.00 NS

C.C: contingency coefficient

CKD (HD): chronic kidney disease on hemodialysis

CKD: chronic kidney disease on conservative treatment

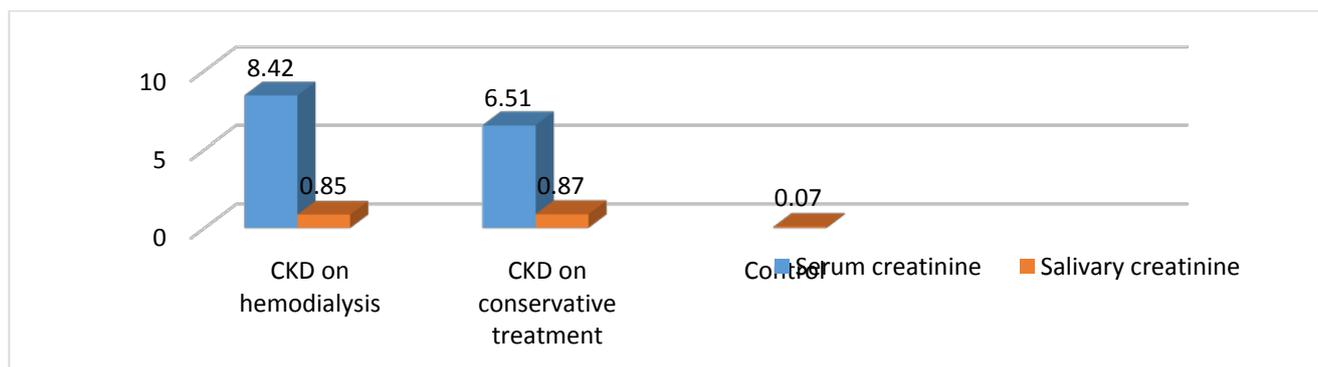


Figure (3): Mean serum and salivary creatinine in CKD patients and control group.

Table (2): Mean salivary creatinine of study groups with ANOVA test.

F: ANOVA

CKD (HD): chronic kidney disease on hemodialysis

Salivary creatinine (mg/dl)	Groups	mean± SD	SE	Range	F	P value
	CKD(HD)	0.85 ± 0.38	0.07	0.36-1.99		
	CKD	0.87 ± 1.22	0.22	0.30- 7.24	11.44	0.00 S
	Control	0.07 ± 0.08	0.01	0.01 - 0.036		

CKD: chronic kidney disease on conservative treatment

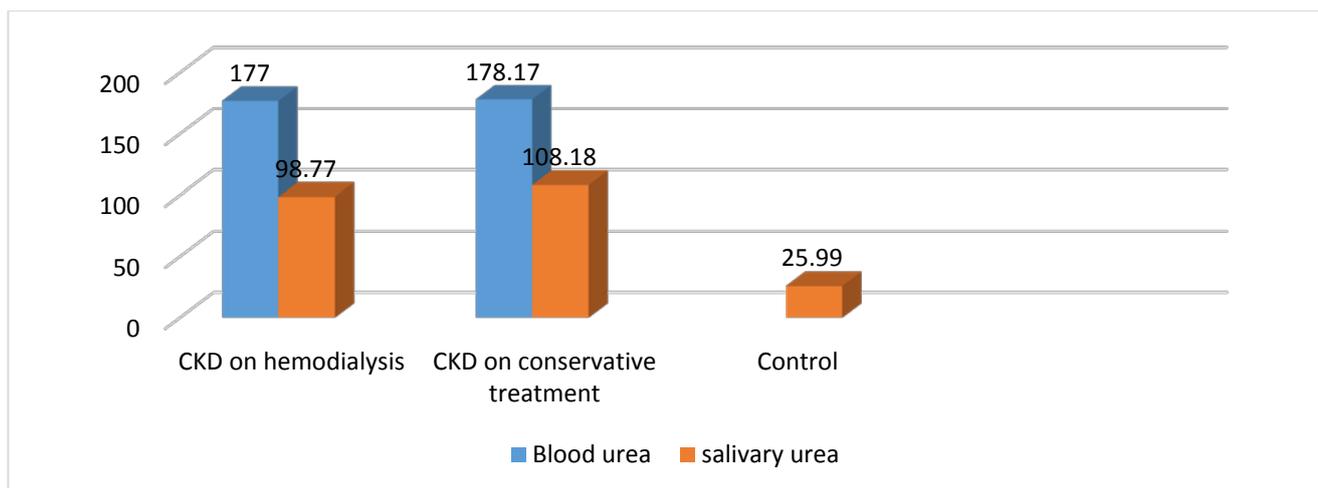


Figure (4): Mean blood and salivary urea in CKD patients and control group.

Table (3): Mean salivary urea of study groups with ANOVA test.

	Groups	Mean ± SD	SE	Range	F	P value
Salivary urea (mg/dl)	CKD(HD)	98.77 ± 28.65	5.23	40.21-159.10	151.69	0.00 HS
	CKD	108.18 ± 18.20	3.32	72.11-141.60		
	Control	25.99 ± 6.94	1.27	15.31- 41.67		

F: ANOVA

CKD (HD): chronic kidney disease on hemodialysis

CKD: chronic kidney disease on conservative treatment

Table (4): Correlation between salivary creatinine and serum creatinine; salivary urea and blood urea in CKD patients.

Groups	Variable		serum Creatinine	Blood urea	
CKD (HD)	Salivary creatinine	r	0.770		
		P	0.000		
	Salivary urea	r			0.860
		P			0.000
CKD	Salivary creatinine	r	0.932		
		P	0.000		
	Salivary urea	r			0.858
		P			0.000

DISCUSSION

Many oral manifestations were seen in both patients' groups. Dry mouth was seen in 46.67% of CKD patients on hemodialysis, this is in agreement with Honarmand et al. (12) who observed 46.7% of hemodialysis patients with xerostomia, but lower than that reported in study conducted by Patil et al. (13) who found 91% of patients were with dry mouth.

In CKD patients on conservative treatment, 36.6% was found with dry mouth, this is lower than that reported by Belazelkovska et al. (14) who found 73.3% of patients were with dry mouth. Dry mouth may be caused by direct gland involvement, fluid restriction, use of medications and mouth breathing (15).

Regarding uremic fetor, 50% of CKD patients on hemodialysis were with uremic fetor. This is almost similar to other studies (16, 17) that mentioned 48.5% and 45% of patients were with uremic breath, respectively.

A study done by Ahmed et al. (15) reported that 66 % of patients were with uremic fetor which is more than what was found in current study.

Patients on conservative treatment, 33.3% were with uremic fetor which is more than that reported by Belazelkovska et al. (14) who was observed 26.6% of patients with uremic fetor.

Uremic fetor, an ammoniacal odor typical of uremic patients, caused by high urea level in the saliva which is decomposed to ammonia by urease. In addition, oral malodor also result from

neglected oral hygiene due to the chronic nature of the disease (18).

In relation to taste change, 43.3% of CKD patients on hemodialysis suffered from taste change. This is almost similar to study done by de la Rosa García et al. (16) who reported 45.5% of patients were with unpleasant taste and exactly similar to Honarmand et al. (12) who observed 43.3% of patients complaining from altered taste.

In those on conservative treatment, 46.6% were with taste change, which is more than that reported by other studies (14, 19) which was 26.66% and 26%, respectively.

Metallic taste in uremic patients has been reported to be due to urea concentration in the saliva and its subsequent decomposition to ammonia and carbon dioxide by urease. The taste change can also be due to the use of medication, metabolic disturbance, diminished taste buds number and changes in the salivary flow and composition. Another study reported that high urea levels, dimethyl and trimethyl amines and low levels of zinc might be associated with decreased taste perception in uremic patients (20, 21).

Concerning pale oral mucosa, 40% of CKD patients on hemodialysis were with pale oral mucosa. This was almost similar to what was reported in study done by Honarmand et al. (12) who found 42.2% of patients were with pale oral mucosa. Patil et al.

(13) mentioned that 87% of patients were with pale oral mucosa, this is more than twice the findings of current study.

In those on conservative treatment, 20% were with pale oral mucosa. This is almost similar to study done by Oyetola *et al.* (19) who found 24% and half in frequency than in a study done by Belazelkovska *et al.* (14) who found that 53.3% of patients were with from mucosal pallor.

Pale oral mucosa secondary to anemia mainly developed due to inability of the failing kidneys to produce erythropoietin, loss of red blood cells through dialysis, reduced red blood cells survival time and their early destruction and, in some cases, from malnutrition (22, 13).

Regarding aphthous ulceration, 23.3% of CKD patients on hemodialysis complained from aphthous ulceration, which is more than those reported in a study done by Ahmed *et al.* (15) who reported 2.8%

In those on conservative treatment, 16.6% were with aphthous ulceration. This is more than those mentioned in study performed by Oyetola *et al.* (19) who reported 2%.

It is well known that aphthous ulcers may occur due to psychological stress of CKD patients especially those on hemodialysis, impaired immune system or nutritional problems such as folic acid or iron deficiency.

Concerning gingival enlargement, 13.3% of CKD patients on hemodialysis were with gingival enlargement in this study. Ahmed *et al.* (15) found that 33.9% of hemodialysis patients were with gingival enlargement which is more than those in current study.

While in those on conservative treatment, 16.6 % of patients complained from gingival enlargement. This is inconsistent with Belazelkovska *et al.* (14) who reported that there was no CKD patients on conservative treatment with gingival enlargement.

Such enlargement can be induced by calcium channel blockers (nifedipine, amlodipine, verapamil, diltiazem) used for management of hypertension in CKD patients. The condition in turn may be aggravated by the neglected oral care (18).

In relation to burning sensation, 6.6% of hemodialysis patients suffered from burning sensation. This is lower than those mentioned in a study done by Ahmed *et al.* (15) who reported 25.7%.

In those on conservative treatment, 10% were with burning sensation, this finding disagrees with Belazelkovska *et al.* (14) who reported that there was no patients on conservative treatment complained from burning sensation.

Predominant reasons for the complaining of burning sensation are xerostomia, the presence of candidiasis, prolonged clearance of medications as well as vitamin deficiency (14).

Regarding of angular cheilitis, 3.3% of hemodialysis patients complained from angular cheilitis. This is almost similar to that reported in study conducted by Murali *et al.* (23) who found 5%. Another study done by Ali *et al.* (17) found 29% of patients were with angular cheilitis.

In those on conservative treatment, also 3.3% were with angular cheilitis. Belazelkovska *et al.* (14) found 46.6% of patients suffered from angular cheilitis which is much more than those in the current study.

It has been found that angular cheilitis associated with candida infection and anemia (15; 24).

No significant difference between CKD patients on hemodialysis and those on conservative treatment regarding all oral manifestations.

A few studies investigating oral manifestations in CKD patients on different treatment modality.

Belazelkovska *et al.* (14) reported that there was a significant difference between hemodialysis patients and those on conservative treatment concerning uremic fetor, burning sensation

and pale oral mucosa. This is inconsistent with the findings of the current study.

In the current study, a significant difference in salivary creatinine and urea among study groups was seen. There was a significant increase in salivary creatinine and urea level in both patients groups compared to control group. This is in agreement with other studies which reported that a salivary creatinine and urea level in CKD patients is higher compared to control group (1, 9, 10, 25, 26). While no significant difference between the two patients groups regarding both salivary creatinine and urea. Also, no significant difference in serum creatinine and urea between the two patients groups.

Increased salivary concentration may be due to increased serum concentration which creates a concentration gradient which in turn increases the diffusion of creatinine and urea from serum to saliva in CKD patients. It is also possible that high level of creatinine and urea in saliva may be an alternative route of excretion in compromised kidney function state (27, 28).

The present study showed that there was a significant positive correlation between salivary creatinine and urea and serum creatinine and urea levels, respectively in both patients groups. This is in agreement with other studies which reported that the levels of creatinine and urea in both saliva and serum were positively correlated in CKD patients (9, 10, 25, 26, 28, 29). This study supported the fact that whenever there was an increase in serum creatinine and blood urea, there would be concomitant increase in salivary creatinine and urea also.

CONCLUSIONS

1. Oral manifestations such as dry mouth, uremic fetor and taste change are the most common oral findings in CKD patients. Pale oral mucosa, aphthous ulceration, gingival enlargement, burning sensation and angular cheilitis are also seen in CKD patients.
2. Salivary creatinine and urea is higher in CKD patients on hemodialysis and those on conservative treatment compared to healthy subjects.
3. A significant positive correlations between salivary and blood creatinine as well as salivary and blood urea in CKD patients. Hence, saliva could be used as alternative noninvasive method for diagnosis and monitoring of CKD.
4. Patients with CKD need comprehensive professional oral care and self-care instructions.

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