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Assessment of oral manifestations of patients with renal failure undergoing hemodialysis by serum and salivary biomarkers

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Abstract

Background: Renal failure refers to a condition where the kidneys lose their normal functionality**.** Patients with end stage renal disease (ESRD) have to undergo hemodialysis (HD), With impaired renal function, a decreased glomerular filtration rate (GFR), and the accumulation and retention of various products of renal failure, the oral cavity may show a variety of changes as the body progresses through an azotemic to a uremic state. The general dentist should be able to recognize these oral symptoms as part of the patient's systemic disease and not as an isolated occurrence.

Aims of the study: To evaluate the biochemical properties of the saliva and Assessment of oral manifestations in patients with chronic renal failure undergoing hemodialysis.

Patients and methods: Spectrophotometer was used for measuring serum and salivary calcium, phosphorous, urea and creatinine in thirty three hemodialysis patients and twenty two control healthy subjects . Salivary PH, Gingival index and salivary buffering capacity was also recorded.

Results and discussion: All serum and salivary biomarkers (calcium, phosphorous, urea and creatinine) were significantly changed in hemodialysis patients (calcium decreased while the others increased).Also salivary PH and buffering capacity were significantly increased in hemodialysis patients. Gingival index also increased, and the oral manifestations that was recorded include: dry mouth (n=21), uremic odor (n=20) , bad taste (n=17) , burning sensation (n=14) , coated tongue (n=10) ,pale mucosa (n=5) petechia (n=3), fissured tongue (n=3).

Conclusions: there was differences in salivary parameters between hemodialysis patients and control group and the salivary variables was correlated too serum variables , many oral manifestations found to be in hemodialysis patients.

Key words: Hemodialysis, Renal Failure, Saliva, Oral Manifestations, Gingival Index, Saliva PH, Saliva Buffering.

Introduction

Renal failure refers to a condition where the kidneys lose their normal functionality, which may be due to various factors including infections,

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auto immune diseases, diabetes, cancer, and toxic chemicals . It is characterized by the reduction in the excretory and regulatory functions of the kidney and it is the ninth leading cause of death in United States as well as most industrialized nations throughout the world. [1,2]

The kidneys have many functions, including regulating the acid-base and fluid electrolyte balances of the body by filtering blood, selectively reabsorbing water and electrolytes, and excreting urine. In addition, the kidneys excrete metabolic waste products, including urea, creatinine, and uric acid, as well as foreign chemicals .[3]

Apart from these regulatory and excretory functions, the kidneys have a vital endocrine function, secreting renin, the active form of vitamin D, and erythropoietin. These hormones are important in maintaining blood pressure, calcium metabolism, and the synthesis of erythrocytes, respectively .[3]

Patients with chronic renal failure have to undergo kidney replacement therapy such as hemodialysis (HD), peritoneal dialysis or renal transplantation. The aim of HD treatment is to remove metabolic waste products such as urea, and to remove excess fluid from the body of the patients to restore circulatory volume.

In studies of renal patients, up to 90% were found to have oral symptoms of uremia. Some of the presenting signs were an ammonia-like taste and smell, stomatitis, gingivitis, decreased salivary flow, xerostomia, and parotitis. [4,5]

In general, oral health is influenced by many factors. Diet, level of oral hygiene, use of fluoride, presence of commensally microorganisms, genetic factors, ageing, systemic diseases, medication and the amount and 'quality' of saliva all have been described to play a pivotal role in the net state of oral health .[6]

The saliva circulating in the mouth at any given time is termed as whole saliva and it comprises a mixture of secretions from the major and minor salivary glands and traces from the gingival crevicular fluid. Saliva definitely promotes oral health and hence lack of its secretion contributes to the disease process. [7,8]

Because of interest in the link between oral and general health, clinicians are increasingly using salivary analyses to diagnose systemic disease and to monitor general health. The reason for this interest lies in the ability of new diagnostic tools, such as sensitive enzyme-linked immunosorbent assays, as well as other technologies(such as using spectrophotometers), to distinguish a range of salivary components that are biomarkers for changes in the body's health.

The noninvasive nature of salivary testing has made it an attractive and effective alternative to blood and urine testing, and home testing kits have made it possible for people to monitor their own health using this diagnostic medium.[9]

The Aims of the study is to evaluate the biochemical properties of the saliva including (salivary flow rate, buffering capacity, calcium, phosphorous, urea and creatinine concentrations) in patients with chronic renal failure undergoing hemodialysis . Assessment of oral manifestations in patients with chronic renal failure undergoing hemodialysis. To correlate the biochemical properties of saliva with that of serum to test the reliability of salivary content as a diagnostic tool in patients with chronic renal failure.

Patients and Methods

Patients

The collection of samples was conducted during the period from **1/2011** to **4/2011**. **Thirty three** patients were taken from the artificial Kidney Unit in Baghdad and Al-Yarmok teaching hospitals in Baghdad city .The patient was previously diagnosed as having renal failure based on the history, clinical examination and renal function test(creatinine increased **3.0** times **or** creatinine >**355** μmol or urine output below **0.3** ml/kg for 24 hours). **Fifteen** were males and **eighteen** were females with female to male ratio of (**1.2: 1**) and their ages ranged from **19** to **75** years.

Control group

The control group consisted of **28** subjects. They were collected from medical staff and relatives who were free from signs and symptoms of renal disease and free from other systemic disease that can have effect on the variables under study like hypertension, diabetes, liver disease, thyroid disease and parathyroid disease. **Fourteen** were males and **fourteen** were females, with male to female ratio (**1:1**) and their ages ranged from **22** to **69** years.

Collection of saliva samples

Samples of Whole Unstimulated mixed (resting) saliva were collected from all participants using standard techniques .[10] Briefly, subjects refrained from eating, drinking, using chewing gum or mints, for at least l hour prior to saliva collection. Two minutes after rinsing the mouth several times with tap water, saliva sample was collected from each individual by simple drooling method while sitting comfortably with the head in an upright position.

All saliva samples were collected between **8.00** and **10.30** A.M. to avoid diurnal variation. The saliva samples then were divided into two plane tubes, one for the evaluation of salivary PH and buffering capacity(**1** ml), immediately after collection,. The other(**1-2** ml) for salivary biomarkers assay centrifuged at **3000** rpm for **10** minutes and kept under deep freeze for future analysis of salivary calcium , phosphorous, urea and creatinine. The collection of saliva was timed so that flow rate(ml/Min) could be determined by dividing the volume of collected saliva(ml) by the time(min).

Collection of serum Samples

Five milliliters of venous blood were drawn from each control individual. Slow aspiration of the venous blood sample via the needle of syringe to prevent hemolysis with tourniquet apply 15cm above the cubital fossa. The samples were dropped into clean disposable tubes, left at room temperature for 30 minutes for clot formation and then centrifuged for **20** minutes at **5000** rpm. The serum was separated and stored in the freeze for future analysis of serum calcium ,phosphorous ,urea and creatinine .

Determination of serum and salivary calcium , phosphorous, urea and creatinine .

All these variables was determined by ultraviolet spectrophotometer by using chemical kits . the laboratory analysis was performed in medical laboratory in Al-Yarmok hospital .

Determination of Saliva pH and buffering capacity and gingival index

Saliva pH was determined immediately after the collection of saliva samples in order to avoid any time related pH changes or loss of CO2. The analysis was performed electrometrically using a hand-hold pH-meter (ALLA, IP57, France). (Figure 1)

Buffering capacity of saliva was evaluated using Ericsson`s method (classical method) ,according to this method ,after measuring salivary PH

the collected saliva was mixed by inverting the tube twice , then **3.0** ml of **.0033** mol/l HCL added to **1** ml of saliva , after mixing for **10** minutes , the final PH in the saliva is evaluated electrometrically .[11] The gingival health condition was assessed using gingival index [12]

Assessment of Oral Manifestations

The assessment of oral manifestations was done in the artificial kidney unit using disposable dental mirror and probe and hand torch , the coated tongue was determined clinically when there is whitish dorsum of the tongue that cannot be removed by rubbing with elongated papillae (Figure 2-A).

The uremic odor was determined when there is a urine odor in the breath , the dry mouth was considered by asking the patient `` do you feel dry mouth frequently `` , the bad taste and burning sensation was determined by directly asking the patient about these symptoms .

Petechia , ecchymosis and pale mucosa was determined by clinical examination .(Figure 2-A and B).

Results

Salivary and serum parameters

There was no significant difference in concentration of salivary calcium between hemodialysis patients and control group. The concentration of salivary phosphorous , urea and creatinine was significantly higher in hemodialysis patients (**Table 1**). The concentration of serum calcium was significantly lower in hemodialysis patients ,while the concentration of phosphorous ,urea and creatinine was significantly higher in hemodialysis patients (**Table 2**).The salivary PH and buffering capacity was higher in hemodialysis patients while the salivary flow rate was significantly less in hemodialysis patients. The gingival index was higher in hemodialysis patients (**Table 3**).

All salivary variables (calcium , phosphorous , urea and creatinine) was significantly related to serum variables for the hemodialysis patients (**Table 4**). There was no correlation between salivary calcium and urea with serum calcium and urea for the control group while the salivary phosphorous and creatinine was significantly related to serum phosphorous and creatinine (**Table 4**)

There was no significant correlation between salivary flow rate and salivary calcium and phosphorous concentrations in the hemodialysis patients while the concentration of salivary urea and creatinine was significantly correlated with salivary flow rate. For the control only the salivary calcium concentration was significantly correlated with salivary flow rate(**Table 5**)

Oral manifestations of hemodialysis patients

The oral manifestations that was found in renal failure patients with dry mouth (n=21), uremic odor (n=20), bad taste (n=17), burning sensation (n=14), coated tongue (n=10), pale mucosa (n=5) petechia (n=3), fissured tongue (n=3) (**Table 6**).

The oral manifestation that was found in control group was dry mouth (n=4), coated tongue (n=3) .fissured tongue (n=1) (**Table 6**).

The salivary flow rate of renal failure patient with coated tongue (mean 0.188 ,S.D 0.0626) showed a significant difference ($p<0.05$) with those without coated tongue (mean 0.247, S.D. 0.089), The salivary urea concentration of renal failure patient with uremic odor (mean 140.75,S.D 38.15) showed a significant difference ($p=<0.05$) with those without coated tongue (mean 128.60, S.D. 36.739) , The salivary urea concentration of

renal failure patient with burning mouth sensation (mean 159.5, S.D 23.88) show a highly significant difference (p=<0.01) with those without coated tongue (mean 115.5, S.D 33.46) The salivary flow rate of renal failure patient with dry mouth (mean 0.199, S.D 0.073) show a significant difference (p<0.05) with those without dry mouth (mean 0.280, S.D. 0.087). (**Table 7**)

Discussion

The concentration of salivary calcium, phosphorous, urea and creatinine in patients with renal failure under hemodialysis.

There was no significant changes in salivary calcium of renal failure patients in relation to control group and this may be due to decreased saliva flow rate in renal failure patients group since salivary calcium is flow dependant .[13]

Earlier studies it was pointed out that concentration of both potassium and calcium are independent of salivary flow rate.[14] but later on this observation was proved to be incorrect and indeed the calcium concentration falls when the salivary flow rate increases.[13]

In this study we found a significant increase of salivary phosphorous in renal failure patients in relation to control group and correlated well with serum phosphorous and this is in agreement with Savica *et al*. [15]. There was a significant increase in salivary urea in renal failure patients in relation to control group and was not correlated l with serum urea and this is in agreement with Dahlberg *et al*.[16]

The concentration of urea in human parotid saliva had previously been shown to be below that of, and proportional to, the concentration of urea in the blood .[17] even surpass the blood level .[18] This increase at low flow rates, usually below 0.5 ml/min, has been attributed to the reabsorption of water in the ducts .[17] Therefore salivary urea levels correlates well with the serum urea so that saliva can be used as a non invasive diagnostic tool .[16,19]

Although total amount of saliva is decreased in hemodialysis patients, [5] urea content is elevated which results in increasing the buffering capacity of saliva and decreasing dental caries particularly in children. [20]

There was a significant increase in salivary creatinine in renal failure patients in relation to control group and correlated with serum creatinine and this is in agreement with Dahlberg *et al*. and Lloyd *et al*. [16,21.] Salivary levels of creatinine share a close relationship with serum levels, with an average concentration 10 times less than serum .[21]

The concentration of serum calcium, phosphorous, urea and creatinine in patients with renal failure under hemodialysis.

In this study we found an increase in serum phosphorous in renal failure patients and this agrees with other studies. [22, 23] and this increase in serum phosphorus may be due to the decrease of the ability of the kidneys to excrete phosphorous normally .[24]

The concentration of serum calcium was decreased in renal failure patients and this agrees with Kleeman *et al*. and Pillitteri. [23,25] , and this decrease in serum calcium may be due to increase in serum phosphorous since there is indirect relationship between serum calcium and phosphorous concentration and any increase in one of them will lead to decrease in the other .[3]

Another possible cause for decrease in serum calcium may be the disturbance in vitamin D synthesis due to renal failure, and this is due to failure of the kidney to synthesis the

active form of Vitamin D (**1,25-dihydroxy cholecalciferol**) which is essential for the absorption of vitamin d in the intestine .[3]

In this study we found that serum urea concentration was significantly higher in renal failure group than in control group and this confirm the result of other studies .[23,26] And this increase in serum urea concentration is due to the fact that urea is concentrated as the basic nitrogenic compound of the metabolic products that are synthesized in the liver and excreted with urine, and in case of renal failure there will be a disturbance of the renal function and this lead to decrease in renal urea excretion thus leading to increase in serum urea concentration.[27]

The serum creatinine concentration was significantly higher in renal failure patients than in control group and this agree with previous studies.[28,29] and this increase in creatinine concentration is due to the fact that creatinine is one of the metabolic byproducts that are excreted normally with urine , and in case of renal failure there is a decrease in GFR which lead to increase serum creatinine .[27,30]

The gingival index , salivary flow rate and saliva buffering capacity of patients with renal failure under hemodialysis.

In this study there is increase of the gingival index in renal failure patients and this disagree with Oshrain *et al* [31]. Previous studies have suggested that the oral hygiene of hemodialysis patients is lower than that of the general population. In a 2-year follow-up study, Locsey reported greater calculus formation, gingivitis, caries, atrophy of the alveolar bone, pathologic tooth mobility proportional to bone resorption and tooth loss, pocket formation and necrotic teeth found under crowns, bridges and fillings[32]. Also in an American study of 45 hemodialysis patients, all had some form of periodontal disease and oral debris, 64% of them had severe gingivitis .[33]

In general, the higher the flow rate, the faster is the clearance and higher the buffer capacity and thus leading to lesser microbial attacks on teeth and gingiva .[34,35]

Unstimulated saliva is essential for the health and well being of the oral cavity and also best as a strong protective effect to the oral cavity, against dental caries [36] . Any unstimulated flow rate below 0.1 ml/min is considered hypofunction .[37]

The significant increase in saliva PH and buffering capacity was due to increase urea concentration, The high pH of unstimulated whole saliva from the patients with renal failure was the result of a higher concentration of ammonia as a resulting from urea hydrolysis. [38] The increased salivary phosphate concentration previously reported in these patients could partially contribute to the higher buffer capacity .[34,39] Ferguson and Botchway have demonstrated that within an individual the circadian variation of calcium, phosphate and pH in both unstimulated and stimulated saliva is considerable[40] . The increase in saliva pH and buffer was in agreement with .[5]

Oral manifestation of patients with renal failure undergoing hemodialysis

More than 30 oral signs and symptoms of patients with renal failure have been reported .[41] In the present study, the most prevalent oral symptoms was dry mouth (63%), taste change (51%), uremic odor (60%) , burning sensation (42%) , white coated tongue (30%) , pale mucosa (21%) , petechia (9%) ,fissured tongue (9%).

In the present study we found a significant correlation between the symptom of dry mouth and the decreased flow rate in renal failure. Dry mouth in patients with ESRD was

reported to be caused by a combination of direct uremic involvement of the salivary glands and dehydration due to the restriction of fluid intake .[34,42] . Epstein *et al*. suggested that salivary flow can be used as a diagnostic index to aid in maintaining renal patients at appropriate fluid balance levels.[34]

In the present study we found a significant correlation between uremic odor and salivary urea concentration The uremic fetor, an ammoniacal odor, is typical of uremic patients and is caused by a high concentration of urea in the saliva; the urea is broken down to ammonia .[38]

Previous reports indicated that sour and sweet tastes were more seriously affected than bitter and salty tastes .[43] Burge *et al* suggested that high levels of urea and dimethyl and trimethyl amines and a low level of zinc might be associated with decreased taste perception in uremic patients .[4]

Tongue and/or mucosal pain and an increase of tongue coating were also detected, and petechia or ecchymosis (or both) in the oral mucosa was found infrequently in the present study .

We found a highly significant correlation between burning mouth sensation and serum urea concentration .Larato reported that the accumulation of ammonia might irritate the oral mucosa, resulting in glossitis and stomatitis, and that oral mucosal changes might be only a phase of a generalized mucosal breakdown .[44]

As we found in this study 9% of renal failure patients showed a petechia sign .Oral bleeding as a result of the use of anticoagulants and quantitative and qualitative changes of platelets in these patient is well known .[41] Gingival bleeding, petechia and echymosis develop in labial and buccal mucosa, soft palate and tongue borders as a result of qualitative and to a lesser degree, quantitative platlet defects [45] Anticoagulants used for hemodialysis can be a predisposing factor.[46]

And as we found in this study 21% of renal failure found to have pale mucosa. pale mucosa result of normochromic/normocytic anemia [47] caused by erythropoietin and folic acid deficiencies. [48] inhibited erythropoiesis, shortened erythrocyte life span, hemolysis and hemodialysis complications .[26,41]

We found a significant relation between coated tongue sign and decreased flow rate Coated tongue has also been described as filiform papillae enlargement, with bacteria accumulation due to factors such as a water-restricted diet, low saliva flow, poor oral hygiene, and even the emotional condition of the dialysis patient . [45,49]

Conclusions

- The concentration of serum urea, phosphorous and creatinine was increased while the concentration of serum calcium was decreased in patients with renal failure under hemodialysis.
- The concentration of salivary urea, phosphorous and creatinine was increased while the concentration of salivary calcium was decreased win patients with renal failure under dialysis.
- The concentration of salivary calcium, phosphorous, urea and creatinine was correlated with serum calcium, phosphorous, urea and creatinine.
- The gingival index was higher in patients with renal failure.
- The salivary ph and buffering capacity was higher in patients with renal failure.
- The salivary flow rate was decreased in patients with renal failure.

- There is more oral manifestations in patients with renal failure.
- The coated tongue sign was correlated with decreased salivary flow rate.
- The uremic odor was correlated with salivary urea concentration.
- The burning mouth sensation was correlated with salivary urea concentration.
- The dry mouth symptom was correlated with decreased salivary flow.

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Table (1) concentration of salivary calcium , phosphorous ,urea and creatinine in hemodialysis patients and control group.

Sig.	p-value	t-test	S.D	Mean	Sample size		
N.S	0.139	1.499	1.45783	2.2379	28	Control	Calcium
			0.95805	1.7709	33	Patient	
H.S	0.000	3.987	2.13007	9.0982	28	Control	Phos
			3.67060	12.2367	33	Patient	
H.S	0.000	13.943	11.71893	31.0000	28	Control	Urea
			37.37140	133.6061	33	Patient	
H.S	0.000	4.769	0.57925	0.3825	28	Control	Creat
			0.56011	1.0797	33	Patient	

N.S : Non Significant at level $P > 0.05$.
H.S : Significant at level $P < 0.01$.

Table (2) concentration of serum calcium , phosphorous ,urea and creatinine in hemodialysis patients and control group.

Sig.	p-value	t-test	S.D	Mean	Sample size		
HS	0.000	5.730	0.81241	9.3232	28	Control	Calcium
			1.43803	7.5667	33	Patient	
HS	0.000	8.380	0.74693	3.6393	28	Control	Phos
			1.68902	6.5300	33	Patient	
HS	0.000	14.683	10.80557	28.5893	28	Control	Urea
			45.04930	156.7576	33	Patient	
HS	0.000	11.812	0.21233	0.9080	28	Control	Creat
			2.53390	6.5885	33	Patient	

H.S : Significant at level $P < 0.01$.
S : Significant at level $P < 0.05$.

Table (3) the gingival index , salivary flow rate , salivary ph and buffering capacity for hemodialysis patients and control group.

Sig.	p-value	t-test	S.D	Mean	Sample size		
S	0.010	2.654	0.53683	0.9043	28	Control	Gl
			0.42222	1.2303	33	Patient	
HS	0.000	4.666	0.13149	0.3605	28	Control	FLOW
			0.08586	0.2297	33	Patient	
HS	0.000	6.963	0.22703	6.4357	28	Control	PH
			0.49939	7.1488	33	Patient	
HS	0.000	11.664	0.36077	5.4521	28	Control	BUFF
			0.52292	6.8185	33	Patient	

H.S : Significant at level $P < 0.01$.
S : Significant at level $P < 0.05$.

Table(4) The correlation of salivary variables to serum variables for the hemodialysis group and for the control group.

Sign.	p-value	r	variable	sample
HS	<0.01	0.511	Serum-salivary calcium	Hemodialysis patients
HS	<0.01	0.510	Serum-salivary phosphorous	
HS	<0.01	0.358	Serum-salivary Urea	
S	<0.05	0.471	Serum-salivary Creatinine	
NS	>0.05	-0.17758	Serum-salivary calcium	Control group
HS	<0.05	0.640777	Serum-salivary phosphorous	
NS	>0.05	0.124412	Serum-salivary Urea	
S	<0.05	0.432729	Serum-salivary Creatinine	

Table(5)The correlation of saliva flow rate to other variables for the hemodialysis patients and control group.

sign	p	r	independent	dependant	sample
NS	>0.05	0.1499	Salivary calcium	Saliva flow rate	Hemodialysis patient
NS	>0.05	-0.1163	Salivary phosphorous	Saliva flow rate	
HS	<0.01	-0.5310	Salivary urea	Saliva flow rate	
S	<0.05	-0.3760	Salivary creatinine	Saliva flow rate	
S	*<0.05*	*0.415202*	*Salivary calcium*	*Saliva flow rate*	Control group
NS	>0.05	0.206332	Salivary phosphorous	Saliva flow rate	
NS	>0.05	-0.27028	Salivary urea	Saliva flow rate	
NS	>0.05	-0.29669	Salivary creatinine	Saliva flow rate	

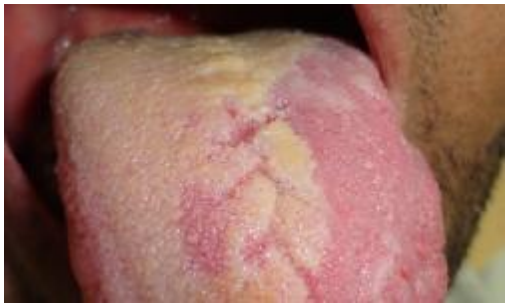
Table (6) oral manifestation of hemodialysis patients and control group.

Salivary variable	Hemodialysis subgroups	No.	Mean(sd)	t-test	p-value	sig
Saliva flow rate	Renal failure patients with coated tongue	10	0.188 (0.0626)	2.199	<0.05	s
	Renal failure patients without coated tongue	23	0.2478 (0.0893)			
Salivary urea	Renal failure patients with uremic odor	20	140.75 (40.988)	<0.05		s
	Renal failure patients without uremic odor	13	111.921 (35.167)			
Salivary urea	Renal failure patients with burning mouth sensation	14	159.57 (23.88)	4.414	<0.01	hs
	Renal failure patients without burning mouth sensation	19	115.5 (33.46)			
Saliva flow rate	Renal failure patients with dry mouth	21	0.19904 (0.073)	2.74253	<0.05	s
	Renal failure patients without dry mouth	12	0.280 (0,087)			

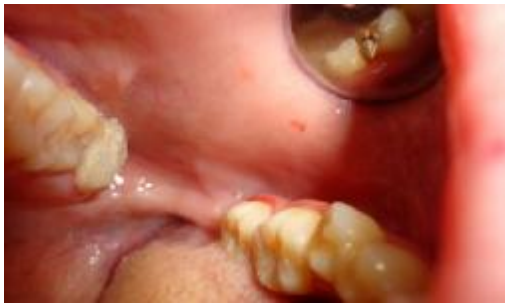
Table (7) the relation of oral manifestations to salivary variables in hemodialysis patients

%	Total	Female	Male	Oral manifestation	group
0.63	21	10	11	**Dry mouth**	Patients
0.60	20	9	11	**Uremic odor**	
0.51	17	11	6	**Bad taste**	
0.42	14	8	6	**Burning sensation**	
0.30	10	3	7	**Coated tongue**	
0.21	7	5	2	**Pale mucosa**	
0.09	3	2	1	**Petechia**	
0.09	3	2	1	**Fissured tongue**	
0.10	3	1	2	**Dry mouth**	control
0.14	4	2	2	**Coated tongue**	
0.03	1	-	1	**Fissured tongue**	

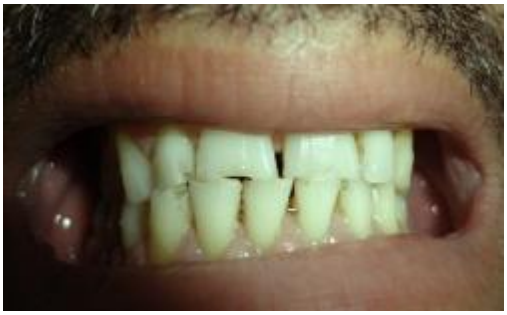
Figure -1- pH meter



A:Coated Tongue



B:Petecchia



C:Pale Mucosa

FIGURE -2- Oral Manifesrations In Hemodialysis Patients