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Oral Manifestation and Caries Experience in Pre-Dialysis Chronic Kidney Disease Patients

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ABSTRACT

Patients with chronic kidney disease (CKD) are prone to develop oral lesions due to the disease process or the therapy or both. The systemic problems started to develop in the pre-dialysis stages of CKD. Oral lesions and caries experience are the non-traditional risk factors in progression of CKD. This research was conducted to study and compare the oral manifestation and caries experience of pre-dialysis patients and healthy subjects in Hospital Universiti Sains Malaysia (HUSM). Fifty-eight patients, which consist of 29 pre-dialysis patients and 29 controls were recruited. CKD patients (stage III and IV) who attended nephrology clinic and CKD Resource Centre Unit of HUSM were selected. The control group consisted of healthy patients without any systemic disease who attended dental clinic of HUSM. The patients were examined for the oral manifestation. The decayed, missing, filled teeth (DMFT) index were also recorded. Oral lesions were present in 96.6% of pre-dialysis patients and 51.7% of control group ($p < 0.001$). The significant oral manifestations in pre-dialysis patients were xerostomia, halitosis, abnormal taste, mucosa pallor, enamel hypoplasia, gingival enlargement and abnormal lip pigmentation. There was significant difference in caries experience between pre-dialysis patients and healthy controls but no correlation between estimated glomerular filtration rate (eGFR) and caries experience in the pre-dialysis patients. Thus, dental screening needs to be done to control the problems. Future studies with multicentred and larger sample size are warranted to explore the magnitude of this problem.

Keywords: *Chronic kidney disease; pre-dialysis; oral manifestation; caries experience*

INTRODUCTION

Chronic kidney disease (CKD) is an irreversible loss of renal function for at least three months and it becomes a major public health problem worldwide (Levey *et al.*, 2003). The overall prevalence of CKD in West Malaysia was 9.07%. The prevalence of CKD by stages I, II, III, IV and V were 4.16%, 2.05%, 2.26%, 0.24%, and 0.36%, respectively (Hooi *et al.*, 2013).

Diabetes mellitus and hypertension are now the major cause of end-stage renal failure worldwide. The other causes include glomerulonephritis, cystic kidney disease and other kidney related inherited diseases (Jha *et al.*, 2013). The symptoms of CKD can be asymptomatic unless if the significantly increase in urea and creatinine in which patient can developed nausea, vomiting, drowsiness and pruritis (Almutary *et al.*, 2013).

CKD have associated oral problems arising due the disease process or the effects of therapy or both. Untreated oral lesions may worsen the clinical presentation and prognosis due to increased systemic inflammatory burden (Wahid *et al.*, 2013). Chronic inflammatory process in the periodontium can increased the inflammatory markers such as cytokines and interleukin in advanced CKD. The elevation of inflammatory markers contributes to inflammatory response that reduces the renal function (Chen *et al.*, 2006). According to previous studies, the incidence of oral symptoms in CKD patients is up to 90% (Saini *et al.*, 2010). CKD is associated with oral clinical manifestation such as periodontitis (inflammation of the supporting structures of the teeth), dry mouth, abnormal taste, halithosis, burning sensation, white patches, red patches, mucositis, oral candidiasis, changes in salivary composition and flow rates, pale mucosa and abnormal pigmentation (Patil *et al.*, 2012; Proctor *et al.*, 2005; Tadakamadla *et al.*, 2014). Furthermore, it is reported that the CKD patients will have increased dental calculus but lower caries rate, and it might be due to high salivary urea and phosphate levels (Akar *et al.*, 2011). However, there is lack of evaluation of the oral manifestation that arises in CKD patients (Zwiech and Bruzda-Zwiech, 2013). Treatment of associated oral lesions especially the inflammation of the gingival using non-surgical periodontal therapy and oral care technique is needed for significant improvement in the CKD status, even though the causal relationship between oral infections and CKD is yet to be fully established (Lockhart *et al.*, 2012).

This study aimed to determine the common oral manifestion and caries experience in pre-dialysis patients (stage III and IV) and compare with healthy controls. There was no study regarding oral manifestation and caries experience in pre-dialysis patients worldwide. Pre-dialysis patients were chosen as these are the stages where the complications and systemic problems arise. We hope that this study will be beneficial for the future early dental referral and intervention in pre-dialysis patients to prevent progression of the disease.

MATERIALS AND METHODS

Subjects

This study was conducted at Hospital Universiti Sains Malaysia (HUSM) in Kubang Kerian, Kelantan, Malaysia. A total of 58 subjects aged 18 years and above, who volunteered to participate in this study were recruited. Twenty-nine study subjects were recruited among the CKD patients of stage III and IV (estimated glomerular filtration rate [eGFR] between 15 and 59) who attended Nephrology Clinic and Chronic Kidney Disease Resource Centre Unit of HUSM. Twenty-nine healthy controls without any systemic diseases who came to visit HUSM dental clinic were recruited as well. The study period was from April to November 2018.

The eGFR is calculated using the Modification of Diet in Renal Disease (MDRD) equation (Levey *et al.*, 2007)

$eGFR = 175 \times (SCr)^{-1.154} \times (age)^{-0.203} \times 0.742$ [if female] $\times$ 1.212 [if Black]

Scr (standardised serum creatinine) = mg/dL

age = years

Subjects who had undergone anti-microbial/ anti-inflammatory therapy in the last six weeks, used steroidal or immunosuppressive drugs, were on statins or iron-replacement therapies, who had undergone periodontal treatment in the last six months, who are pregnant/lactating women or women on hormone-replacement therapy were excluded from the study.

Ethical Issues

Ethical clearance was obtained from Human Research and Ethics Committee of USM (USM/JEPeM/18010032).

Questionnaire

Subjects who met the inclusion criteria were informed about the study, then a signed consent was obtained. Information on subjects' biodata, relevant medical history, drug history, residential area, alcohol and tobacco consumption was recorded. Then, subjects were asked about oral symptoms which included dry mouth (xerostomia), the abnormal taste, bad breath (halitosis), mucosal pain, gum bleeding and burning sensation in the mouth (burning mouth).

Oral Examination

Subjects were then examined on dental chair under adequate light which was performed by one well-trained undergraduate dental student under the supervision of a periodontist and medical specialist who calibrated the clinical examination and the reliability testing also had been done using kappa test. Any presence of oral changes such as abnormal lip pigmentation, oral candidiasis, tongue coating, mucosal pallor, lip and mouth ulceration, mucosal red and/or white lesion, petechial haemorrhage, gingival enlargement soft tissue hyperpigmentation and enamel hypoplasia was recorded. The oral mucosa assessment was based on the WHO Guide to Epidemiology and Diagnosis of Oral Mucosal Diseases (Kramer *et al.*, 1980). The Decayed, Missing, Filled Teeth (DMFT) index was also charted for each subject.

Statistical Analysis

The data collected was analysed using SPSS (version 24.0, IBM). Continuous variables were presented in mean and standard deviation whereas categorical variables were presented in number and percentage. Chi-square analysis was used to determine the significance of distribution of categorical variables between groups. Comparison of DMFT scores between control and study subjects was analysed using Mann-Whitney U test. Spearman's correlation was used to correlate DMFT index and eGFR in pre-dialysis patients. The level of significance was set at $p < 0.05$.

RESULTS

Subjects Characteristics

Of the 58 patients who participated in this study, 34 (58.6%) of them were male and 24 (41.4%) of them were female. The average age of the study subjects was 62.93 (11.97) years, which is much higher than that of the healthy controls 29.69 (11.46) years, the difference was highly significant ($p < 0.001$). The study subjects (93.1%) and the healthy controls (79.3%) were of Malay ethnicity; however, the difference was not statistically significant (Table 1).

Table 1 Sociodemographic factors

Characteristics	All n=58	CKD patients n=29	Controls n=29	*p* value
Average age (SD)	**46.31 (20.40)**	**62.93 (11.97)**	**29.69 (11.46)**	0.000*
Gender [n (%)]				
Male	34 (58.6)	22 (75.9)	12 (41.4)	
Female	24 (41.4)	7 (24.1)	17 (58.6)	0.008*
Ethnicity [n (%)]				
Malay	50 (86.2)	27 (93.1)	23 (79.3)	
Non-Malay	8 (13.8)	2 (6.9)	6 (20.7)	0.253
Occupation [n (%)]				
Working/retired	38 (65.5)	24 (82.8)	14 (48.3)	
Unemployed	20 (34.5)	5 (17.2)	15 (51.7)	0.006*
Education level [n (%)]				
Secondary education	25 (43.1)	16 (55.2)	9 (31.0)	
Tertiary education	33 (56.9)	13 (44.8)	20 (69.0)	0.063
Medical comorbidity [n (%)]				
Hypertension	28 (48.3) 30 (51.7)	28 (96.6) 1 (3.4)	0 (0.0) 29 (100.0)	0.001*
Diabetes mellitus	18 (31.0) 40 (69.0)	18 (62.1) 11 (37.9)	0 (0.0) 29 (100.0)	0.001*
Heart diseases	11 (19.0) 47 (81.0)	11 (37.9) 18 (62.1)	0 (0.0) 29 (100.0)	0.000*
Gouty arthritis	4 (6.9) 54 (93.1)	4 (13.8) 25 (86.2)	0 (0.0) 29 (100.0)	0.112
Hyperlipidaemia	7 (12.1) 51 (87.9)	7 (24.1) 22 (75.9)	0 (0.0) 29 (100.0)	0.010*
Medication [n (%)]				
Taking	29 (50.0)	29 (100.0)	0 (0.0)	
Not taking	29 (50.0)	0 (0.0)	29 (100.0)	0.000*
Smoking status [n (%)]				
Past and current smokers	18 (31)	12 (41.4)	6 (20.7)	
Non-smoker	40 (69)	17 (58.6)	23 (79.3)	0.089
Alcohol intake [n (%)]				
Yes	2 (3.4)	2 (6.9)	0 (0.0)	0.491
No	56 (96.6)	27 (93.1)	29 (100.0)	
Residential area [n (%)]				
City	43 (74.1)	15 (51.7)	28 (96.6)	
Rural area	15 (25.9)	14 (48.3)	1 (3.4)	0.000*

*$p < 0.05$, statistically significant

Oral Manifestations

Mucosa pallor was the most common oral manifestation seen in pre-dialysis patients, which it involved 75.9% of the patients. There were significant difference findings between pre-dialysis patients and controls in xerostomia (44.8%), halitosis (55.2%), abnormal taste (27.6%), enamel hypoplasia (37.9%), gingival enlargement (24.1%) and abnormal lip pigmentation (27.6%) (Table 2).

Table 2 Oral soft tissue lesions

Characteristics	All n=58	CKD patients n=29	Controls n=29	*p* value
Oral lesions [n (%)]	43 (74.1)			
Present		28 (96.6)	15 (51.7)	
Absent		1 (3.4)	14 (48.3)	0.000*
Burning mouth [n (%)]	1 (1.7)			
Present		1 (3.4)	0 (0)	
Absent		28 (96.6)	29 (100)	1.000
Abnormal taste [n (%)]	9 (15.5)			
Present		8 (27.6)	1 (3.4)	
Absent		21 (72.4)	28 (96.6)	0.025*
Bleeding gums [n (%)]	22 (37.9)			
Present		11 (37.9)	11 (37.9)	
Absent		18 (62.1)	18 (62.1)	1.000
Halitosis [n (%)]	21 (36.2)			
Present		16 (55.2)	5 (17.2)	
Absent		13 (44.8)	24 (82.8)	0.003*
Xerostomia [n (%)]	14 (24.1)			
Present		13 (44.8)	1 (3.4)	
Absent		16 (55.2)	28 (96.6)	0.000*
Mucosal pain [n (%)]	8 (13.8)			
Present		7 (24.1)	1 (3.4)	
Absent		22 (75.9)	28 (96.6)	0.052
Oral candidiasis [n (%)]	1 (1.7)			
Present		1 (3.4)	0 (0)	
Absent		28 (96.6)	29 (100)	1.000
Tongue coating [n (%)]	4 (6.9)			
Present		3 (10.3)	1 (3.4)	
Absent		26 (89.7)	28 (96.6)	0.611
Mucosa pallor [n (%)]	22 (37.9)			
Present		22 (75.9)	0 (0)	
Absent		7 (24.1)	29 (100)	0.000*

(*Continued on next page*)

Table 2 (*Continued*)

Characteristics	All n=58	CKD patients n=29	Controls n=29	*p* value
Ulceration [n (%)]	6 (10.3)			
Present		3 (10.3)	3 (10.3)	
Absent		26 (89.7)	26 (89.7)	1.000
Red/white lesion [n (%)]	3 (5.2)			
Present		3 (10.3)	0 (0)	
Absent		26 (89.7)	29 (100)	0.237
Petechial haemorrhage [n (%)]	4 (6.9)			
Present		4 (13.8)	0 (0)	
Absent		25 (86.2)	29 (100)	0.112
Enamel hypoplasia [n (%)]	11 (19.0)			
Present		11 (37.9)	0 (0)	
Absent		18 (62.1)	29 (100)	0.000*
Gingival enlargement [n (%)]	7 (12.1)			
Present		7 (24.1)	0 (0)	
Absent		22 (75.9)	29 (100)	0.010*
Abnormal lip pigmentation [n (%)]	8 (13.8)			
Present		8 (27.6)	0 (0)	
Absent		21 (72.4)	29 (100)	0.004*
Hyperpigmentation of oral soft tissues [n (%)]	5 (8.6)			
Present		4 (13.8)	1 (3.4)	
Absent		25 (86.2)	28 (96.6)	0.352

*$p < 0.05$, statistically significant

Caries Experience

There were significant differences of caries experience between pre-dialysis patients and controls in terms of missing teeth (MT), filled teeth (FT) and DMFT scores. However, we do not observe significant difference in decayed teeth (DT) scores between both groups (Table 3). No correlation has been observed between caries experience and eGFR of pre-dialysis patients (Table 4).

DISCUSSION

In the present study, oral lesions were reported in 96.6% of the pre-dialysis subjects, which was consistent with previous studies that reported similar prevalence in CKD patients; 100% (Patil *et al.*, 2012) and 96.7% (Oyetola *et al.*, 2015) respectively.

In the present study, mucosa pallor was the most common oral sign that was seen in 75.9% of the CKD patients. When compared to the control group that had no occurrence, the statistic was highly significant. This observation is consistent with previous study in Karnataka, India where mucosal pallor was reported in 87% of the stage IV CKD patients (Patil *et al.*, 2012). Oral mucosal pallor is seen in CKD patients secondary to anaemia, which occur mainly due to reduced erythropoietin production by the kidneys, iron and vitamin deficiency, malnutrition, inflammation, platelet dysfunction, reduced red blood cell survival and haemolysis. As previously reported in a study conducted in HUSM, the prevalence of anaemia was

Table 3 Caries experience of pre-dialysis patients and controls

Variable	Median (IQR)		Z statistic	*p* value
	CKD patients	Controls		
Decayed	3.00 (4)	4.00 (5)	−1.454	0.146
Missing	8.00 (12)	0.00 (2)	−4.376	0.000*
Filled	0.00 (2)	2.00 (3)	−2.403	0.016*
DMFT	13.00 (11)	9.00 (9)	−2.642	0.008*

*$p<0.05$, statistically significant

Table 4 Correlation between eGFR and caries experience

	Decayed		Missing		Filled (F)		DMFT	
	r	*p* value	r	*p* value	r	*p* value	r	*p* value
eGFR	−0.086	0.657	0.091	0.639	−0.093	0.630	0.064	0.741

Spearman's correlation.

75.8% in pre-dialysis chronic kidney disease patients and increased significantly with deteriorating renal function (Salman *et al.*, 2016).

Enamel hypoplasia was present in 37.9% of the study group but none in control group. However, previous study did not report significant difference (Patil *et al.*, 2012). Uraemia which commonly occurs in CKD patient, will result in teeth with enamel hypoplasia and brownish discolouration during development of dentition (Patil *et al.*, 2012). The location of hypoplastic enamel in the permanent teeth corresponds with age at onset of CKD (Al-Nowaiser *et al.*, 2003). It has been suggested that hypocalcaemia secondary to chronic kidney disease that contributes to renal osteodystrophy is one of the causes of enamel hypoplasia (Koch *et al.*, 1999).

As compared to a study conducted in Nigeria where abnormal lip pigmentation was the most commonly reported oral signs in CKD patients (Oyetola *et al.*, 2015), the present study reported lower prevalence; however, the difference is still significant. This condition might be probably due to the failure of beta-melanocyte stimulating hormone being excreted from the kidneys. As a result, excess melanin is deposited at the basal layer of oral epithelium (Kolla *et al.*, 2012). Lip pigmentation may be induced by ultraviolet light and is common in older individuals (Çerman and Altuna, 2016). Ethnic pigmentation and smoking habit may play a role in influencing the results of this study. Based on a study on Malaysian and Thai population, it has been found that there were significant differences in oral pigmentation frequency between ethnic groups, where the frequency in Malay population was 91%, Chinese 74% and Indians 96% (Hedin and Axéll, 1991). In individuals where genetic factors stimulate melanocytes, these cells also have the capacity to increase melanin production further if influenced by tobacco (Hedin and Axéll, 1991).

In the present study, gingival enlargement was observed in 24.1% of CKD subjects. Previous study did not report significant difference of this oral sign between CKD patients and healthy controls (Oyetola *et al.*, 2015). Gingival enlargement in this case can be caused by drugs, which can be discussed as three major groups: anticonvulsant (phenytoin), immunosuppressive agents (cyclosporine A) and calcium channel blockers. Among calcium channel blockers, nifedipine is the drug that has higher frequency of causing gingival enlargement (6.3%), followed by verapamil (4.1%) and amlodipine with lower rates (1.3% to 3.3%)

(Aldemir *et al.*, 2012). As 96.6% of CKD patients are having hypertension, there was high possibilities of usage of calcium channel blockers. The exact reason of drug-induced gingival hyperplasia is not known; however it is believed that this condition is associated with some risk factors that contribute gingival inflammation such as poor oral hygiene, presence of dental plaque, the dose and duration of the drug used (Matharu *et al.*, 2005).

Xerostomia was the most commonly reported oral symptoms in this study, affecting 44.8% of the CKD subjects. Other studies reported different prevalence of 91% (Patil *et al.*, 2012) and 12.22% (Oyetola *et al.*, 2015) respectively. It has been suggested that complaint of xerostomia or dry mouth in CKD patients is due to fluid restriction, electrolyte imbalance, the use of certain medications such as frusemide and hydrochlorothiazide (anti-hypertensives), mouth breathing secondary to lung perfusion problems, and possible salivary gland alteration (atrophy of minor salivary glands' parenchyma) which resulted in reduced saliva secretion (Kaushik *et al.*, 2013).

Halitosis was presented as an oral complaint in 55.2% in the present study subjects. Similarly, other studies reported significant difference between CKD patients and control group where 34% of study group patients complained of halitosis (Patil *et al.*, 2012). The uraemic fetor or bad breath reported by CKD patients is an ammoniacal odour, which is caused by a high concentration of urea in the saliva, and it is broken down into ammonia (Mahdi *et al.*, 2012). This is due to the reduced function of kidneys to excrete urea out of the body, hence there is increased concentration of urea in the blood (uraemia) as well as in the saliva. Besides, CKD patients often neglected their oral hygiene (Kaushik *et al.*, 2013).

Abnormal taste was present in 27.6% of patients in study group and 3.4% of patients in control group ($p < 0.05$). Previous studies have reported alteration in taste in 42% (Patil *et al.*, 2012) and 26% (Oyetola *et al.*, 2015) of the CKD subjects. It has been reported that high levels of urea, dimethyl and trimethyl amines and low levels of zinc might be associated with decreased taste perception in uremic patients (van der Eijk and Allman-Farinelli, 1997). Increased concentration of urea in saliva that is broken down into ammonia and carbon dioxide by salivary urease give that metallic taste sensation (Kho *et al.*, 1999).

For caries experience, the decayed score demonstrated non-significant differences between CKD patients and healthy controls in the present study ($p = 0.146$). CKD patients had significantly more missing teeth than the healthy control. Conversely, CKD patients also had significantly less filled teeth compared to controls the DMFT scores of CKD patients were significantly higher than control group.

The present results were comparable to a study in Thailand that evaluated DMFT index between CKD patients of different stages (Ausavarungnirun *et al.*, 2016). The number of missing teeth and DMFT index was significantly higher in CKD stage III patients when compared with their control group which consists of CKD stage I and II patients (Ausavarungnirun *et al.*, 2016).

A different study in Vietnam also found that the DMFT and number of missing teeth in the CKD patients (stage III to V) was significantly higher than the non-CKD group (Pham and Le, 2019). The average age of CKD patients was higher than healthy control and number of missing teeth accounted in the DMFT index was influenced by increasing age (Pham and Le, 2019). Another study on haemodialysis patients also reported high mean DMFT which shows a significant correlation with patient's age (Nascimento *et al.*, 2018). A previous study also reported that the percentage of totally edentate subjects and the mean number of missing teeth was higher among the patients than the controls, particularly in the pre-dialysis group patients;

and the factors potentially involved in tooth loss include age and low socio-economic status (Sobrado Marinho *et al.*, 2007), which can be regarded as the confounding factor in the present study.

There were various studies that reported contradictory research findings with the current study in which the prevalence of active caries and fillings was lower in the CKD patients (stage III to V) than the healthy controls, particularly in the patients with advanced CKD (stage V) and the number of decayed and filled teeth did not differ significantly between CKD patients and healthy controls (Sobrado Marinho *et al.*, 2007). The CKD patients also presented lower caries experience in addition to less decayed and missing teeth than the control group (Tadakamadla *et al.*, 2014). However the results were differed due to the different stages of CKD patients which focusing on the haemodialysis group. There was a lower index of restorations in haemodialysis patients; however, the result was not statistically significant (Bayraktar *et al.*, 2004). Additionally, there was no differences in the number of fillings between haemodialysis patients and healthy controls; and the number of decayed teeth in haemodialysis patients was similar to healthy controls (Bots *et al.*, 2006).

There were few limitations in this study. The mean age for CKD group was much higher compared to healthy controls. As DMFT index increases with age (Oral Health Division, 2004), this might be one of the factors to explain the significant difference in DMFT index between the groups. DMFT index is also less useful in predicting caries experience in patients where the missing teeth may be due to periodontal disease but not solely due to caries, which will lead to eventual overestimation of the caries experience (Seman *et al.*, 2007).

In the present study, we found that there was no correlation between eGFR and DMFT scores of the pre-dialysis patients. There was disagreement in the present study with a study on the correlation of kidney function and DMFT index that showed significant positive correlation; however, that was not a good predictive value. In that study, Pham and Le (2019) used the Cockcroft-Gault formula to estimate the creatinine clearance value. However, that formula does not give the best eGFR as what CKD-EPI and MDRD formulas did as Cockcroft-Gault formula is additionally influenced by body weight and BMI (Michels *et al.*, 2010). DMFT index is greatly influenced by increasing age (Thorman *et al.*, 2009). The lack of correlation between eGFR and decayed, missing, filled and DMFT scores is due to relatively small sample size and limitation of the eGFR value in which the predialysis group was taken from patients with eGFR value of 15 to 59 only.

CONCLUSION

The oral manifestation and caries experience are common in predialysis patients and this interrelationship should be taken as consideration for early dental care and prophylaxis in all predialysis patients to prevent deterioration of oral health that subsequently affects the progression of the disease.

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DECLARATION

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