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Oral Manifestations in Different Stages of Chronic Kidney Disease

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Abbreviations:

CKD: Chronic Kidney Disease; HD: Hemodialysis; PD: Peritoneal Dialysis; P-D: Pre Dialysis; ESRD: End-Stage Renal Diseases

1. Abstract

1.1. Background: Chronic kidney disease is a progressive, slow and silent disease characterized by kidney damage and a consequent reduction of kidney function. The final stage indicates that renal function is lost and necessitates renal replacement therapy for survival. This progression is associated with worsening symptoms and complications in oral cavity. The aim of this study was to investigate oral manifestations in patients with chronic kidney disease according to which stage of the disease for early detection, that alterations play an important point for dental guide during that progression.

1.2. Methods: The present study was a quantitative observational study of 450 patients, 150 control, 100 cases of patients in pre-dialysis, 100 cases of patients in treatment with peritoneal dialysis, 100 cases of patients in treatment with hemodialysis, from a Hospital in the north of Portugal, Oporto. An oral exam was performed for detection oral manifestations, age, smoking, alcoholic and hygiene habits, systemic diseases were collected.

1.3. Results: Oral lesions were presente in the four study groups, but with more incidence in the hemodialysis group. Comparing the groups studies, we found a significant finding in presence of xerostomia (45.0%), gingivitis (68.0%), petechiae (10.0%), ecchymoses (17.0%), mucosa paleness (46.0%), uremic breath (29.0%), burning mouth (9.0%), which increased as the treatment time of chronic kidney disease (peritoneal dialysis and hemodialysis) increased.

1.4. Conclusion: A multidisciplinary team should follow this patient, from pre-dialysis phase to kidney transplantation, the oral cavity must have important and continuous monitoring, as the early detection of lesions and specific oral manifestations could be a means of early diagnosis of chronic kidney disease or its progression.

1.5. Clinical trial registration: The trial was retrospectively registered with the Clinical Trial Registry with identifier number NCT06487689 registered on 11/06/2024.

2. Background

In the past decade, the number of patients with chronic kidney disease (CKD) is increasing worldwide, and is started to be considered a public health problem. It is well established the risk factors for people with CKD, that include people with uncontrolled diabetes, cardiovascular disease, uncontrolled high blood pressure and people with age > 60 years [1]. The Kidney Disease Outcomes Quality Initiative defined the CKD based on the presence of kidney damage or glomerular filtration rate (GFR) (GRF < 60 ml/min per 1.73 m2 for 3 months or more) and was classified into five stages based on the level of GFR [2]. The CKD at the beginning might be asymptomatic and some patients could have dental treatments or oral diseases related to undiagnosed early CKD. If the dental care have basic knowledge about oral lesion/manifestations of CKD, it will help to refer undiagnosed renal failure and facilitate a safe dental treatment [3]. In stages 1-3 of CKD, the patients don't have any contraindication for routine dental treatment, while patients with advanced kidney disease (stages 4-5) required special considerations (complex medical treatment, anemia, risk of bleeding, hypertension, infections, treatment) [4]. A study demonstrated the prevalence of CKD for each stage: for stage 1 (pre-dialysis (P-D)) is 3.5%, for stage 2 is 3.9%, for stage 3 is 7.6%, for stage 4 is 0.4% and for stage 5 it is 0.1%. This prevalence rates indicated that dental care providers will treat patients in any stage of CKD [5], but with more kidney lesions the dental treatment started to be more complex and the decisions of the type of treatment of the teeth/lesion more important [6]. The last two stages [4-5] the patients needs renal replacement therapy, dialysis. It is aggressive measures but is a life-saving intervention that has significantly prolonged life expectancy. The dialysis can be two types: hemodialysis (HD) and peritoneal dialysis (PD) [7]. Considering the prevalence of CKD stages 1-5 and CKD stages 3-5, in the European population were contemplate differences [8]. In the USA, in an adult population, the prevalence of CKD stage 3-5 was 4.8% - 11.8% [9]. Recently a study indicated a prevalence the 5.6% - 9.9% of CKD across 11 countries, in a population of 2.4 million CKD patients [10]. In a study [11], the prevalence of CKD (stage III-V) in Portuguese population was the 6.1%, and more recently another study concluded the prevalence of CKD (stage I-V) in Portuguese population is the 20.9% [12]. It was estimated that 90% of CKD patients have oral symptoms and lesions. However, with the new dialysis technology many of the oral manifestations are less seen [11]. Oral diseases is a potencial and preventable cause of poor health outcomes in people with CKD, can also be as a result or consequence of the disease itself or/and a side effects of is treatment of PD or HD. Generally, people with CKD needs more oral healthcare but use less the dental service, they neglected oral health [13]. The oral care of CKD patients can be difficult because of the kidney disease and also the diseases associated like a diabetes and hypertension [14]. The oral mucosa of patients with CKD, specially in end-stage renal disease (ESRD), become more susceptible to appears pathologic or infectious lesions, associated and with more incidence with the kidney function declines. This is occurs due the metabolic alterations (water-electrolyte changes, calcium-phosphate imbalance), the consequences related to the CKD itself, deficiencies in the immune system [15]. Oral manifestations in CKD involve: mucosal and glandular tissues, gingival and periodontal apparatus, maxilar and mandibular bone and dental status. The oral clinical manifestations will depends on the stage of the CKD and type of treatment. The association between the CKD (type of peritoneal treatment and/or stage of CKD) and oral health status is steal not very clear in the current literature [16,17]. Oral mucosal alterations in CKD may take different forms, colors or manifestations, such as pallor of the mucosa, uremic odor, xerostomia, taste disorders, petechiae, periodontitis, tongue coating, mucosal ulcers, gingivitis, dental calculus, caries, uremic stomatitis, candidiasis and lichen plano [18-21]. Malnutrition is present in CKD due to the dietary restriction of the disease itself, which leads to impaired smell and taste, leading to weight loss. The taste disorders may be influenced by these patients have dry mouth, provoked by alterations in salivary gland function in CKD patients; the presence of low zinc levels in the saliva, serum and leukocytes; the high urea concentration in this patients is common [22]. Some studies report that in patients with CKD the concentration of salivary uric acid increases together with the reduction of the salivary flow rate, with the consequence that the presence of uremic fetor may occur [23]. In patients with CKD, the prevention of halitosis is very important, since it can cause discomfort, psychosocial embarrassment and negatively affect the quality of life [24]. Xerostomia is a sensation of dry mouth, which is relatively common in patients with CKD because is a result of the restriction in drink excess fluids, the effect of some medications (frusemide and hydrochlorothiazide), electrolyte imbalance, possible salivary gland alteration and oral breathing secondary [25]. The patients with End-Stage Renal Disease (ESRD) have a hight incidence of taste disorders and xerostomia, with more prevalence in HD [26]. Patients with CKD with hypo-salivation normally exhibit glossitis, cervical caries, cracked, candidiasis, dry buccal mucosa and peeled and atrophic lips [27]. However, is also important remember that periodontal disease may caused infections that can afecte the peritoneum and causing peritonitis. Periodontitis is a chronic, degenerative and inflammatory disease and is characterized by the disorder of biofilm ecology that leads to a gradual and irreversible destruction of the support structure of the tooth, periodontium (gengiva, periodontal ligament, cementum and alveolar bone), and consequently loss the tooth [28,29]. Periodontitis is consider a silent public health problem because of its hight prevalence (28-31) and is the most common non-communicable chronic inflammatory disease. Is associated with significant medical and dental care costs, had and negative impact on quality of life and systemic health, alterations on masticatory function, aesthetics and

speech [28,30,32,33]. A local inflammation in observed in periodontitis tissues and this inflammation can affects body systems by changing the inflammatory mediators in the blood levels, expand the possibility of systemic inflammation in dialysis patients [34] and cause a peritonitis, that in severe cases can lead to death [35]. Some recent studies demonstrated a positive correlation between oral condition, with more incidence in periodontite, and patients with CKD, specially in ESRD [20]. Nephrologists might face oral diseases that are not so easily to identify due the differential diagnoses and alterations that are exclusively dental. Also dentists are not recognized of health changes associated with CKD in patients. The diagnosis and treatment of oral mucosa pathologies should be carried out by a multidisciplinary team [14,18]. The aim of this study was to investigate oral manifestations in patients with CKD for early detection, that alterations play an important point for dental guide during the progression and type of treatment of CKD (PD and HD).

3. Methods

3.1. Study Design

This was a quantitative observational study comparing oral lesions in the patients with or without CKD attending to the nephrology consult, hemodialysis treatment, or dental treatment consult, according to the group, in the Hospital Universitário de Santo António, EPE (CHUdSA), in Oporto, Portugal.

3.2. Participants

This study analyzed patients treated in consults of the Stomatology and Maxillofacial Surgery Service and Nephrology Service at the Centro Hospital Universitária de Santo António, EPE (CHUdSA), in Oporto, Portugal. Patients were appeal with verbal and written information about the study. Those who consequently showed interest in participating in the study, depending of whether they were included in the study criteria, were subjected to screening according to the following criteria.

3.3. Inclusion and Exclusion Criteria of Patients

Subjects selected were with age more than 18 years and less than 80 years, with no change of medication in the last three months and with history of CKD comported by data laboratory (GRF<60 ml/min/1.73m²) managed by the Nephrology Service. The control group only differ in the way they were selected, when they went to a routine dental treatment, and were clinically without CKD. The exclusion criteria were age less than 18 years and than 80 years, patients undergoing orthodontic therapy, patients taking drugs and patients that changes the medication or introduced a new medication. Patients were carefully informed through oral and written explanations about the objective and procedures of the study and who agreed to participate in the study were invited to sign an informed consent form. The patients were evaluated through a questionnaire and a clinical examination of the oral cavity.

3.4. Settings and Location Data

It is a convenience sample collected at the Stomatology and Maxillofacial Surgery Service and Nephrology Service (Centro Hospitalar Universitário de Santo António, Oporto), the group control was patients that were recruit when they went to dental treatment at consuls of stomatology from the Stomatology and Maxillofacial Surgery Service and the study group that were recruit when they went to treatment of CKD or routine consults of nephrology from the Nephrology Service at the Hospital Geral de Santo António, Oporto, Portugal.

3.5. Study Intervention

A questionnaire was made specially for our study the according and with the approved of the Scientific Commission of the Centro Hospitalar Universitário de Santo António, were filled for each patient, the dental information, age, gender, smoking status, alcoholic habits, oral hygiene habits, the diagnosis of CKD, the stage of CKD, current level of GRF, and association with diabetes and hearth diseases that was ask directly to the patient and the medical and biochemical parameters information were collected from the medical reports of the hospital.

In the study group, patients were examined on a stretcher, with the artificial light of a flashlight and with the help of a dental mirror and a periodontal probe CP12. In the control group, it was performed in a dental chair, with direct artificial light, during the morning, with a mirror aid and a periodontal probe CP12.

The periodontal status was performed to each patient to have periodontal information and diagnosis and the oral cavity was observed by a dentist. Some oral lesions finding were confirmed with the dental clinic information of the hospital.

3.6. Clinical Outcomes and Measures

The successive variables were drawing from the patient's medical history: sex (qualitative variable); age (nominal variable); type of CKD (qualitative variable), time with CKD (nominal variable), time of treatment (nominal variable), according of the data provided by the department of Nephrology of the Hospital Sto. António and according the classification of KDIGO; smoking habits (qualitative variable); alcohol habits (qualitative variable); oral lesions/manifestations: pallor of the mucosa, uremic odor, xerostomia, taste disorders, petechiae, periodontitis, tongue coating, mucosal ulcers, gingivitis, dental calculus, caries, uremic stomatitis, candidiasis and lichen plano (qualitative variables), according the oral exam realized by the investigator.

3.7. Sample Size

The trial design it was constituted with 449 patients divided into a control group of 149 patients, and three study subgroups (100 patients in pre dialysis (P-D), 100 patients in PD, 100 patients in HD). The sample is representative of the expected population (international studies indicate that there is a prevalence of CKD in

the Portuguese population of 6.1% (11) of patients with CKD for a margin of error of 5.7% and a significante level of 95%.

3.8. Statistical Analyses

The data were analyzed using IBM® SPSS® Statistics Software (Statistical Program for Social Sciences), Version 29.0 for Windows. Descriptive statistics were used to estimate the frequencies, percentages, averages , standard deviation of participants' sociodemographic characteristics, means, median, standard deviation, minimum and maximum. Qui-square test were performed to compare tabagic, alcoholic, oral hygiene habits, sisthemic diseases (hypertension and diabetes) and CKD time among the 3 groups under study (HD group, PD group and P-D group). Qui-square tests were also performed to evaluate the relationship between the presence/absence of lesions of the oral musosa and the group of belonging. The Shapiro-Wilk test was used to assess the normality of the study groups. Data normality led to the adoption of parametric analysis. To compare the number of decayed, missing and filled teeth between the 3 groups (HD, PD and P-D), ANOVA was used, followed by the Bonferroni test. The effect sizes for the ANOVA were determined using the η2 values, considering the thresholds η2 = 0.01 for a small effect, η2 = 0.06 for a medium effect and η2 = 0.14 for a large effect. For all analyzes, the level of statistical significance was established α <.05.

4. Results

4.1. Demographic Characteristics and Habits

Four hundred and forty-nine individuals were selected for the study according to the inclusion and exclusion criteria, in 100 HD patients, 100 in PD and 100 in P-D and 149 in control group;149 patients, 80 men and 69 woman, constituted the control group and the study group include 300 patients, 152 were men and 148 woman. One patient in the control group withdrew after signing the consent form due to lack of time. As for the behavioral factors that modify or aggravate the disease (Table 1), the smoking habits of our population sample were analyzed and it was found that 351 (78.2%) were non-smokers, 48 (10.7%) ex-smokers and 50 (11.1%) respectively smokers, and there was a statistically significant relationship between smoking and CKD ($\chi2(12)=55.210$; $p<0.001$). With regard to alcoholic habits of the 87 individuals who consume alcohol, 27 (31.0%) are in the P-D group, 24 (27.6%) in PD, 18 (20.7%) in the HD group, 18 (20.7%) in the group control, having verified a statistically significant relationship between alcoholic habits and CKD ($\chi2(2)=13.431$; $p=.016$) and predialysis group and the occasional alcohol consumption. Regarding oral hygiene habits, 354 (78.8%) of participants brush their teeth 1 to 2 times day, 87 (19.4%) between 3 to day and 8 (1.8%) less than once. With regard to the brushing method, the most used is the Bass method (54.3%), but with values very similar to the Stillman Modified method (44.8%). The auxiliary brushing means are used by a small percentage of individuals (n=124; 27.6%), 23 (18.5%) of the control group, 42 (33.9%) of the HD group, 30 (24.2%) of the PD group and 29 (23.4%) of the P-D group, regardless of the most widely used group is elixir.

4.2. Relationship between Systemic Diseases (hypertension and diabetes) and CKD

The table 2 demonstrate that hypertension is present in 116 of individuals, 35.0% in HD, 32.0% of individuals in PD and 36.0% of individuals in P-D, and this relationship is statistically significant ($\chi2\ (3) = 185.405$; $p < .003$).

When we analyze the presence or not of diabetes according to the degree of chronic kidney failure and the control group, it was found that regardless of the group, most individuals had diabetes (87.8%), of the individuals who had this condition, 91.0% were in HD, 90.0% of individuals in PD, 84.0% of patients in P-D and 38% of patients in the control group.and this relationship is statistically significant ($\chi2\ (3) = 185.405$; $p < .003$).

Table 1: Age, gender, smoking, alcoholics, oral hygiene habits in healthy patients, HD, PD,P-D

	N	%	N	%	N	%	N	%	p
Age	52.37	8.88	53.94	13.8	55.12	15.34	61.3	14.65	.001*
Sex									
Female	69	46.3	53	53	49	49	46	46	0.712
Male	80	53.7	47	47	51	51	54	54	
Smoking Habits									
Non Smoking	133	89.3	72	72	69	69	77	77	
Smoking 1-10per/day	9	6	11	11	5	5	3	3	
Smoking 11-20per/day	4	2.7	10	10	1	1	3	3	.001*
Smoking > 21per/day	0	0	1	1	1	1	2	2	
Ex-Smoking	3	2	6	6	24	24	15	15	
Alcoholic Habits									
Non ingest	131	87.9	82	82	76	76	73	73	
Ingest Occasionally	18	12.1	18	18	23	23	27	27	0.037
Ingest Risk	0	0	0	0	1	1	0	0	

Brushing Technique									
Indeterminate Technique	2	1.3	0	0	0	0	2	2	
Modified Technique Stillman	73	49	47	47	46	46	35	35	0.211
Bass Technique	74	49.7	53	53	54	54	63	63	
Oral Hygiene Habits									
< 1time/day	2	1.3	0	0	3	3	3	3	
1-2 time/day	121	81.2	81	81	77	77	75	75	0.586
> 3 time/day	26	17.4	19	19	20	20	22	22	
Auxiliary Brushing Means									
Absent	126	84.6	58	58	70	70	71	71	
Interdental brush	6	4	5	5	5	5	5	5	
Dental Wire	3	2	0	0	5	5	1	1	.001*
Elixir	8	5.4	37	37	19	19	21	21	
Easy-floss	1	0.7	0	0	1	1	1	1	
Electric Brush	4	2.7	0	0	2	2	1	1	
Tongue Scraper	0	0	0	0	0	0	0	0	
Mouthpiece	1	0.7	0	0	0	0	0	0	

Summary data such as frequency and percentage; p - value derived from the Chi-square test between the four study groups; *: statistically significant

Table 2: Relationship between the presence/absence of hypertension and diabetes and the group under study.

	Study Group				
	Control	HD	PD	P-D	p
Hypertension					
Absent	136 (91.3%)	65 (65.0%)	68 (68.0%)	64 (64.0%)	.003*
Present	13 (8.7%)	35 (35.0%)	32 (32.0%)	36 (36.0%)	
Diabetes					
Absent	111 (74.5%)	9 (9.0%)	10 (10.0%)	16 (16.0%)	.003*
Present	38 (25.5%)	91 (91.0%)	90 (90.0%)	84 (84.0%)	
Total (n)	149	100	100	100	

Summary data such as frequency and percentage; p - value derived from the Chi-square test between the four study groups. *: statistically significant.

4.3. Relationship between CKD time and Type of Treatment

It was found that 70.0% of individuals who do peritoneal dialysis, 67.0% of those in P-D and 47.0% of those who have HD, have chronic renal failure for over 6 years, and this relationship has been statistically significant ($\chi2$ (8) = 19.93; p = 0.011). Only a small minority (5.0%) have chronic renal failure for less than 1 year (Table 3).

When we compare treatment time according to the type of treatment (Table 4), it was found that of the 100 individuals in HD, 30.0% have been in treatment since 1-2 years, 24.0% for over 6 years, 22.0% Less than 1 year, 17.0% between 2 and 4 years and 7.0% between 4 and 6 years. Of the 100 individuals who perform PD they are almost equitable in different treatment times, ranging from 19.0% less than 1 year ago and between 2 to 4 years, 20.0% for over 6 years and 21.0% between 1 2 years and 4 to 6 years, respectively. There was no statistically significant relationship between treatment time and type.

Table 3: Relationship between chronic renal failure and treatment type.

Treatment Type					
Time CKD	HD	PD	P-D	$\chi2$	p
<1 year	2 (2.0%)	1 (1.0%)	2 (2.0%)		
1-2 years	8 (8.0%)	5 (5.0%)	6 (6.0%)		
2-4 years	18 (18.0%)	11 (11.0%)	7 (7.0%)	19.93	0.011*
4-6 years	25 (25.0%)	13 (13.0%)	18 (18.0%)		
>6 years	47 (47.0%)	70 (70.0%)	67 (67.0%)		
Total	100	100	100		

N = frequencies; % = percentage; $\chi2$ = Qui-squared; p = p-value. *: statistically significant.

Table 4: Relationship between treatment time and treatment type.

	Treatment Type			
Treatment Time	HD	PD	χ2	p
< 1 year	22 (22.0%)	19 (19.0%)		
1-2 years	30 (30.0%)	21 (21.0%)		
2-4 years	17 (17.0%)	19 (19.0%)	9.28	0.054
4-6 years	7 (7.0%)	21 (21.0%)		
>6 years	24 (24.0%)	20 (20.0%)		
Total	100	100		

N = frequencies; % = percentage; χ2 = Qui-squared; p = p-value.

4.4. Evaluation of Oral Mucosa Injuries and their Relationship with the Degree of CKD

When we evaluate the presence of oral mucosa injuries according to the degree of CKD (Table 5), we found that of the 28 patients with petechiae in the oral cavity, 10 (35.7%) were in HD, 10 (35.7%) in P-D and 8 (28.6%) in PD, this relationship is statistically significant (χ2 (3) = 15.288; p = .002). There was no cases of petechiae in control group. With regard to oral mucosa pallor, firstly according to clinical observation of the pallor of the oral mucosa and gums and later confirmed with laboratory analysis of hemoglobin, it was present in 42.6% of HD patients, 33.3% in PD and 17.6% in P-D, 6.5 % in control group, and this relationship is statistically significant (χ2 (3) = 66.363; p <0.001). There was also a statistically significant relationship between the presence of ecchymoses and the degree of CKD (χ2 (3) = 10.913; p = .012), and these were present in 63.0 % of HD patients, 22.2 % in P-D and 14.8 % in PD. As for candidiasis (white lesion), it is present in 5 patients, with 2 (40.0%) in HD, 2 (40.0%) in PD and 1 (20.0%) in P-D. No cases of candidiasis were observed in the control group.

The geographical tongue was found in 11 (28.2%) HD patients, 9 (23.1%) in PD and 6 (15.4%) in P-D, 13 (33.3%) in control group. The fissured tongue was found in 3 (37.5%) patients in PD and 3 (37.5%) in control group, 1 (12.5%) in HD and 1 (12.5%) in P-D. Of the 3 individuals who have a pillow tongue are in P-D, and this relationship is statistically significant (χ2 (3) = 10.540; p =0.032). Gingival hyperplasia is present in 13 patients, 2 in HD and P-D, respectively, 4 in PD and 5 in control group. Xerostomia is one of the oral mucosa injuries that has a higher prevalence, and this relationship is statistically significant (χ2 (3) = 27.567; p <0.001), being present in 35.2% of patients in HD, 24.2% in PD, 23.4% in P-D and 17.2% in control group. With regard to uremic breath, it reaches the highest prevalence in HD patients (54.7%) compared to patients in PD (32.1%) and P-D (13.2%), this relationship is statistically significant (χ2 (χ2 (3) = 53.156; p <.001). Enamel hypoplasia assumes greater prevalence in individuals in HD (53.8%) and the lowest prevalence in P-D patients (15.4%). There was a relationship is statistically significant (χ2 (χ2 (3) = 10.14; p =0.017) between angular cheilitis and the study's group, being present in 9 (34.6%) of HD patients, 8 (30.8%) in P-D, 7 (26.9%) in control group and 2 (7.7%) in PD patients, and this relationship is statistically significant (χ2 (χ2 (3) = 10.14; p =0.017). Of the 11 individuals with burning mouth, 9 (81.8%) are HD patients, and this relationship is statistically significant (χ2 (2) = 15.1; p <.001). Regarding the uremic stomatitis lesions, herpes simplex and median romboid glossitis, these are only present in a patient in HD, respectively. Macroglossia is present in 2 patients, one in HD and one in PD, and this relationship does not reach statistical meaning. When we compared only the 3 study groups (HD, PD, P-D) there are some similar oral lesions statistically significant like in the 4 study groups (control, HD, PD, P-D, Control group) (petechiae (χ2 (2) = 7.47; p = .024), paleness of mucosa (χ2 (2) = 18.84; p <.001), ecchymoses (χ2 (2) = 8.89; p = .012), uremic breath (χ2 (2) = 20.86; p <.001), burning mouth (χ2 (2) = 15.1; p <.001), gingivitis (χ2 (2) = 19.52; p <.001)). Periodontitis when is compared only between the 3 study group is statistically significant, being 62.0% in pacientes in HD and P-D, and 47.0% in PD (χ2 (2) = 6.12; p = .047).

4.5 Relationship between the Presence/Absence of Gingivitis and Periodontitis According to the Degree of CKD

The Table 6 shows the presence/absence of gingivitis according to the group under study. It was found that gingivitis reached the highest prevalence in HD patients (31.8%), followed by patients in PD (19.6%) and P-D patients (18.6%), the group control patients was 30.0%, these differences being statistically significant (χ2 (2 (2) = 19.52; p <.001). When we relate periodontitis to the degree of CKD (Table 6), it was found that it is present in 62.0% of patients in HD and P-D respectively, 47.0% of patients in PD and 61.1% of patients in control group, and this relationship was not statistically significant.

Table 5: Relationship between the presence of oral mucosa lesions and the belonging group

	Control Group	HD Group	PD Group	P-D Group		
	(n = 149)	(n = 100)	(n = 100)	(n = 100)	$\chi 2$	p
Petechiae						
Absence	149 (100.0)	90 (90.0)	92 (92.0)	90 (90.0)	15.288	.002*
Presence	0 (0.0)	10 (10.0)	8 (8.0)	10 (10.0)		
Paleness of mucosa						
Absence	142 (95.3)	54 (54.0)	64 (64.0)	81 (81.0)	66.364	< .001*
Presence	7 (4.7)	46 (46.0)	36 (36.0)	19 (19.0)		
Ecchymoses						
Absence	149 (100.0)	83 (83.0)	96 (96.0)	94 (94.0)	10.913	0.012
Presence	0 (0.0)	17 (17.0)	4 (4.0)	6 (6.0)		
Candidiasis						
Absence	149 (100.0)	98 (98.0)	98 (98.0)	99 (99.0)	ns	0.374
Presence	0 (0.0)	2 (2.0)	2 (2.0)	1 (1.0)		
Geographic tongue						
Absence	136 (91.3)	89 (89.0)	91 (91.0)	94 (94.0)	ns	0.66
Presence	13 (8.7)	11 (11.0)	9 (9.0)	6 (6.0)		
Fissured tongue						
Absence	146(98.0)	99 (99.0)	97 (97.0)	99 (99.0)	ns	0.661
Presence	3 (2.0)	1(1.0)	3 (3.0)	1(1.0)		
Pillow tongue						
Absence	149 (100.0)	100 (100.0)	100 (100.0)	97 (97.0)	10.54	0.032
Presence	0 (0.0%)	0 (0.0)	0 (0.0)	3 (3.0)		
Gingival hyperplasia						
Absence	144 (96.6)	98 (98.0)	96 (96.0)	98 (98.0)	ns	0.773
Presence	5(3.4)	2 (2.0)	4 (4.0)	2 (2.0)		
Xerostomia						
Absence	127 (85.2)	55 (55.0)	69 (69.0)	70 (70.0)	27.567	< .001*
Presence	22 (14.8)	45 (45.0)	31 (31.0)	30 (30.0)		
Uremic stomatitis						
Absence	149 (100.0)	99 (99.0)	100 (100.0)	100 (100.0)	ns	0.321
Presence	0 (0.0)	1(1.0)	0 (0.0)	0 (0.0)		
Enamel hypoplasia						
Absence	147 (98.7)	100 (100.0)	96 (96.0)	93 (93.0)	10.687	0.013
Presence	2 (1.3)	0 (0.0)	4 (4.0)	7 (7.0)		
Angular cheilitis						
Absence	142 (95.3)	91 (91.0)	98 (98.0)	92 (92.0)	10.14	0.017
Presence	7 (4.7)	9 (9.0)	2 (2.0)	8 (8.0)		
Lichen plants						
Absence	148 (99.3)	98 (98.0)	98 (98.0)	99 (99.0)	ns	0.74
Presence	1 (0.7)	2 (2.0)	2 (2.0)	1(1.0)		
Burning mouth						
Absence	148 (99.3)	91 (91.0)	99 (99.0)	100 (100.0)	23.616	< .001*
Presence	1 (0.7)	9 (9.0)	1(1.0)	0 (0.0)		
Uremic breath						
Absence	149 (100.0)	71 (71.0)	83 (83.0)	93 (93.0)	53.156	< .001*
Presence	0 (0.0)	29 (0.0)	17 (17.0)	7 (7.0)		

Herpes simplex						
Absence	149 (100.0)	99 (99.0)	100 (100.0)	100 (100.0)	ns	0.321
Presence	0 (0.0)	1(1.0)	0 (0.0)	0 (0.0)		
Median rhomboid glossitis						
Absence	149 (100.0)	99 (99.0)	100 (100.0)	100 (100.0)	ns	0.321
Presence	0 (0.0)	1(1.0)	0 (0.0)	0 (0.0)		
Macroglossia						
Absence	149 (100.0)	99 (99.0)	99 (99.0)	100 (100.0)	ns	0.475
Presence	0 (0.0)	1(1.0)	1(1.0)	0 (0.0)		

ns: p >.05; N = frequencies; % = percentage; $\chi 2$ = Qui-squared; p - value derived from the Chi-square test between the four study groups. *: statistically significant

Table 6: Relationship between the presence/absence of gingivitis/periodontitis and the group under study.

	Control Group	Study Group				
		HD	PD	P-D	$\chi 2$	p
Gingivitis						
Absent	85 (57.0%)	32 (32.0%)	58 (58.0%)	60 (60.0%)	19.52	< .001*
Presence	64 (43.0%)	68 (68.0%)	42 (42.0%)	40 (40.0%)		
Periodontitis						
Absent	58 (38.9%)	38 (38.0%)	53 (53.0%)	38 (38.0%)	-	0.077
Presence	91 (61.1%)	62 (62.0%)	47 (47.0%)	62 (62.0%)		
Total	149	100	100	100		

N = frequencies; % = percentage; $\chi 2$ = Qui-squared; p - value derived from the Chi-square test between the four study groups. *: statistically significant.

4.6. Comparison of the Number of Decayed, filled and Missing Teeth

When we compared the number of teeth with caries between the 3 groups (table 7), we found that the group of patients on HD had significantly higher mean values (0.56 ± 0.83), compared with the group on PD (0.37 ± 0.98) and the group on P-D (0.26 ± 0.60) (F (2; 297) = 3.34; p = .034), these differences assume statistical significance between the HD and P-D groups (p = .030). With regard to the number of teeth filled, the results follow the same trend, with the HD group presenting significantly higher values (5.61 ± 3.46) compared to patients on P-D (3.46 ± 2.51) and PD (3.31 ± 3.61) (F (2; 297) = 15.91; p < .001), these differences are established between the groups: HD and PD (p < .001), HD and P-D (p <.001) and between DP and P-D (p <.001). As for the number of missing teeth, the P-D group had significantly higher mean values (11.36 ± 8.45), followed by the PD group (9.06 ± 9.54) and the P-D group (6.74 ± 7.17) (F (2; 297) = 7.48; p <.001), and these differences assume statistical significance between the HD and P-D groups (p < .001).

Table 7: Comparison of the number of decayed, missing and filled teeth between the cases groups

									HD v/s PD	HD v/s P-D	PD v/s P-D
		N	Min	Máx	Mean ± SD	F	p	η2	p	p	p
Teeth with Caries	HD	100	0	5	0.56 ± 0.83						
	DP	100	0	8	0.37 ± 0.98	3.34	0.034	0.023	0.306	0.03	0.99
	PD	100	0	3	0.26 ± 0.60						
Filled Teeth	HD	100	0	17	5.61± 3.46						
	DP	100	0	15	3.31 ± 3.61	15.9	< .001	0.097	< .001	< .001	< .001*
	PD	100	0	14	3.46 ± 2.51						
Missing Teeth	HD	100	0	26	6.74 ± 7.17						
	DP	100	0	27	9.06 ± 9.54	7.48	< .001	0.048	0.159	< .001	0.165
	PD	100	0	27	11.36 ± 8.45						

Data summarized as minimun, maximum, mean and standard deviation, F statistics and p -value derived from ANOVA and p -values derived from Bonferroni test. *: statistically significant

5. Discussion

In our study the little higher prevalence of CKD in men is in line with some studies (36,37), they also indicated the prevalence of late-stage CKD stages is slightly higher in men and are believed to progress more faster to ESKD than women (37), we only observe this in PD with 51.0% were men but in HD group were only 47.0%. The fast decline of the renal function in men is not know but several theories have been suggested, such the action of sex steroids, metabolism of nitrogen oxide and the specific differences of the sex in the oxidative stress [38].

Our population of patients with P-D CKD when compared with other studies was a little older (median age: 61,30 years) this is important because a new study of Raffray et al., found a gender gap in primary care in the 16-60 years old population, and the <60 years old patients it tends to disappear [39]. CKD alterations occurs more especially in the end-stage and leads to various oral changes. In the oral cavity the alterations are in the teeth, oral mucosa and periodontium. In the present study, oral lesions were found to be significantly more common in the end-stage renal states (PD and HD patients) [40]. The oral mucosa of patients in the last stages of CKD tend to present pathological changes, with a higher incidence of changes in taste, xerostomia among other pathological changes [26]. This is also observed in our study, where we observed that xerostomia had an incidence of 45 (41)% in HD patients and 31% in PD patients, coinciding with studies of Bossola et al., and Jamieson et al. [41,42].

A study by Malekmakan et al., observed a high prevalence of xerostomia (48.6%) and taste disorders (49.3%) in HD patients (43). Chuang et al., found a higher prevalence of burning mouth, taste disorders, and xerostomia in HD patients with diagnosed diabetes [44]. Similar than our study, Dembowska et al., found oral mucosal lesions in 52% of the HD group and only 25 in control group, being xerostomia the most common (22% in HD group), taste disorders (14% in HD group and 1% in control group), burning mouth (11% in HD group), herpes labial (4% in HD), white lesions (2% in HD and 1% in control group), and with only 1% in HD group was found black hairy tongue and lesions on the trauma background (18). In addition to enamel hypoplasia, bad odor, oral hairy leukoplakia, uremic stomatitis, oral malignancy, and gingival hypertrophy are also reported [25]. The demographic characteristics of the studied the average age of our study was 55,6 years and was a very similar representativeness of female individuals (n = 217; 48.3%) and male (n = 232; 51.7%) between the 4 groups, is in the line with some studies [45,46]. Our study demonstrated a relationship between consume alcohol (87 individuals who consume alcohol, 27 (31.0%) are in the P-D group, 24 (27.6%) in PD, 18 (20.7%) in the HD group, 18 (20.7%) in the group control and smoking (351individuals (78.2%) were non-smokers, 48 (10.7%) ex-smokers and 50 (11.1%) respectively smokers) and CKD, like others studies, evidence the association of smoking in the progression to renal failure and end-stage renal disease, being a risk factor in the evolution of CKD (47,48).

Regarding oral hygiene habits, 233 (77.7%) of participants brush their teeth 1 to 2 times day, 61 (20.3%) between 3 to day and 6 (2.0%) less than once. The auxiliary brushing means are used by a small percentage of individuals, 42 of the HD group, 30 of the PD group, 29 of the P-D group and 23 of the control group regardless of the most widely used group is elixir. The relationship between CKD and the decreased oral hygiene habits exist and with more prevalence in end-stage renal disease (HD and PD patients) (49). Gürkan et al., refer a hight percentage of HD patients that do not brushed their teeth regularity (40%) (50). Ruospo et al. [51] in a study in patients with CKD describe that 11.4% rarely brushed their teeth and 25.6% do not use toothbrush [51]. This lake of oral hygiene care in CKD patients maybe is caused by the complications and physical problems of CKD, low understanding of the benefits of oral health care in CKD, high treatment oral costs, bleeding and gum infections, lack of oral health guidelines, lack of social support. Maybe if in the initial stages of CKD the patients received the support, information, and encouragement from the family, friends and doctors to continue the behaviors related to dental care, in the HD stage the oral health would be better protected to infections and the appear of oral lesions [52,53]. Worse oral hygiene and higher number of development enamel defect findings are in agreement with other studies [54]. Patients with hypertension increases the risk to predispose CKD, especially undiagnosed or/and untreated hypertension [55]. We demonstrate that hypertension is present in patients with CKD (35.0% in HD, 32.0% in PD, 36.0% in P-D and 8.7% in control group), with more prevalence in end-stage renal stages when compered with control group. Diabetes mellitus is a major cause of CKD and some research has established a relation, as a risk factor, between diabetes mellitus and CKD, and with a high incidence in end-stage renal disease, that we demonstrated in our study with 91.0% in patients in HD, 90.0% in patients in PD and 84.0% in P-D patients, when compared with 25.5% os patients in control group [46]. CKD patients can suffer from spontaneous gingival bleeding, probably caused by bacteriemia and the platelet dysfunction and aggravated by anemia and the anticoagulants, that cause vessel fragility that leads to the formation of petechiae, ecchymosis and gingivitis. In our study we found 28 patients with petechiae, being 35.7‰ in HD patients, and 23 patients with ecchymosis (63.0% HD patients) like others studies but we have a high incidence [56]. The gingivitis is frequent in patients in dialysis treatment, when compared with earlier stages of CKD, we identify 110 pacientes with gingivitis (PD and HD stage) and only 40 pacientes in P-D stage [56,57]. Xerostomia is a symptom of oral dryness that can be caused by hypofuntion of the salivary glands, with reduces salivary flow secondary to atrophy and fibrosis of the salivary glands. Patiens with xerostomia normally

presents glossitis, candidiasis, cervical caries, fissures, dry mouth mucosa, atrophic lips, difficult chewing, speaking and swallow, taste alterations, we also see this results in our study [41,45,58]. The presence of high incidence of xerostomia, dry mouth and oral burning are more common in CKD patients, with more incidence in HD group [42,59]. We identify xerostomia in patients in HD (35.1%), 24.2% in PD, 23.4% in P-D and oral burning in 81.8% of HD patients [18,45]. It occurs partly due to the medication or caused by the fluid intake restriction and patients in dialysis can be due to the restriction of the fluid intake, which is necessary to accommodate the reduced excretory capacity of the kidney [60]. A significantly lower number of patients were diagnosed with candidiasis (5 patients being 2 in HD and PD group), lichen planus (4 HD, 2 PD, 1 P-D and 1 patient group control), herpes simplex (1% HD), uremic stomatitis (1% HD), angular cheilitis (34.6% HD, P-D, 30.8% PD and 7.7% group control), geographic (28.2% HD, 23.1% PD and 15.4% P-D group), fissured (37.5% PD and control group, 12.5% in HD and P-D group) and hairy (100.0‰ P-D group) tongue, macroglossia (50% HD and 50% PD) and median rhomboid glossitis (100‰ HD) (56,59). Mohammadi F et al. [61] found a prevalence of Candida, a difference species of Candida beings the most prevalent the Candida albicans, in oral cavity of patients with CKD during treatment with HD [61]. Some investigations refers the presence of mucosal pallor in CKD patients is secondary to the anemia precipitated by a lack of erythropoietin production, diminution red cell survival times and bone marrow depression [56]. In the present study, subjects presented with different manifestations like paleness of mucosa (42.6% in HD patients, 33.3% in PD, 17.6% in P-D and 6.5% in control group), enamel hyperplasia (53.8% in HD, 30.8% in PD and 15.4% in P-D group) and gingival hyperplasia (38.5% control group, 30.9% in PD and 15.4% in HD and P-D group), that correlates with the oral findings among others studies [56].The mucosa of patients with CKD in end-stage renal disease have tendency for taste disorders, affected by high urea concentration and low zinc levels. Halitosis and uremic odor are the more frequent in HD patients because the increase levels of salivary urea, dimethyl and trimethylamine, metabolic disorders, medications, changes in saliva composition and salivary flow rate [62]. In our study some of patients have uremic odor, 54.7% in the HD group, 32.1% in PD group and 13.2% in P-D group, and this is similar to those described by Bots et al. [63] and Garcia et al [63,26]. In a study on HD patients, was identify a high prevalence of taste disorders (49.3%) and xerostomia (48.6%) [43]. Dembowska et al. [64] find taste disorders like xerostomia (22%), taste disorders (145%) and burning mouth (11%) in the HD group [18].

Periodontitis can lead to change in systemic conditions and also be influenced by some pathologic conditions, and has been associated with many chronic noncommunicable diseases. The associations that exist are more related to type 2 diabetes mellitus, rheumatoid arthritis, osteoporosis and pregnancy, but other conditions are being taking in count such obesity, respiratory diseases, Alzheimer´s disease, dementia, auto-immune alterations, severe presentation of acute COVID-19 and some cancers [64]. Our study don't find a relationship between periodontal and CKD (patients in HD, DP and P-D), when compared with group control. However, other studies contradict our results and support the relation between CKD and periodontitis [14,20,65-67]. One of the limitations of our study was that the presence of CKD was only excluded in the control group, as the presence of other systemic diseases may also be the cause or consequence of some lesions present in the oral cavity. In HD patients (62.0%), periodontitis is much more common than the PD (47.0‰) and is associated with poor patients malnutrition, poor oral hygiene, and higher inflammatory markets in the blood [68]. As CKD progress the periodontitis increase, but in our study that don't happens, we have periodontitis found 62.0% in HD and P-D patients, when compared with PD (47.0%) patients, but there was not a relationship statistically significant [69]. This result may be because of factors that predispose and speed up the progression of periodontal disease. This factors include hyposalivation and patients with others comorbidities like hypertension and diabetes [70].

Grubbs et al. [71] hypothesized that the relationship between periodontitis and CKD is because the blood circulating of periodontal bacteria that could went to kidney endothelium and make damage, like in cardiovascular disease [71]. In CKD the alterations in the endothelium occurs in the beginning of the disease, and progression with the evolution of the disease, leading to cardiovascular complications [72]. Another possibility is that bacterias from periodontitis could rise and worse the CKD, by damage the endothelium of the kidneys. This bi-directional mechanisms are still remains unclear [21]. In the recent literature, missing teeth and dental caries have a high incidence in CKD in dialysis treatment, patients under HD were found to have a high prevalence of dental caries, like we found in our study the mean values on HD group (0.56 ±0.83) when compared with PD (0.37 ±0.98) and P-D (0.26 ±0.60) groups. This may be a consequence of poor oral hygiene, carbohydrate intake, alteration on the composition of the saliva and is pH, the higher risk of infection in CKH patients, the alteration of the oral microflora [73,74]. Moreover, studies regarding the oral health of mild to moderate kidney diseases should be a research priority and the oral health of CKD should be taken care of.

6. Conclusion

A multidisciplinary team should follow the CRD patient, whenever possible, from the P-D phase to kidney transplantation, to allow a better quality of life and general treatment, where the oral cavity should be inserted. The oral cavity must have important and continuous monitoring, as the early detection of lesions and specific oral manifestations could be a means of early diagnosis of CKD or its progression. As the CKD treatment time increases, some oral

lesions will be more likely to appear, making it important for these patients to have regular dental check-ups.

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8. Declarations

8.1. Ethical Approval and Consent to Participate and Trial Registration

The study was approved by the Ethics Committee of Centro Hospitalar Universitário de Santo António, EPE (CHUdSA) (approval number 132/10(085-DEFI/125-CES)) and was conducted in accordance with the ethical guidelines of the 1964 Declaration of Helsinki on experimentation involving human subjects. Written informed consent was obtained from all the participants in the study. Personal data and the name of the patients in all the study were always kept anonymous and did not appear in any document during the study or any publication.

The study was regístrate as a clinical trial in Clinical trial.gov Protocol Registration and Results System no. NCT06487689. It was retrospectively registered on 11/06/2024.

9. Consent for publication

Not applicable.

10. Competing Interests

The authors declare no conflict of interest.

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