SALIVARY FUNCTION AND BIOMARKER PROFILES IN RELATION TO ORAL HEALTH IN PATIENTS WITH PRE-DIALYSIS CHRONIC KIDNEY DISEASE

Georgiana Florentina Gheorghe[1], Laura Iosif[2*,] Oana Elena Amza[1*], Bogdan Dimitriu[1†], Liliana Gârneaţâ[3], Alexandra Ripszky Totan[4], Ana Maria Cristina Ţâncu[2]

1. Department of Endodontics, Faculty of Dentistry, Carol Davila University of Medicine and Pharmacy, 010232 Bucharest, Romania;
2. Department of Prosthodontics, Faculty of Dentistry, Carol Davila University of Medicine and Pharmacy, 010232 Bucharest, Romania;
3. Department of Internal Medicine and Nephrology, "Carol Davila" University of Medicine and Pharmacy, 050474 Bucharest, Romania;
4. Department of Biochemistry, Faculty of Dentistry, "Carol Davila" University of Medicine and Pharmacy, Dionisie Lupu Street, No. 37, 020021 Bucharest, Romania.

* Correspondence: laura.iosif@umfcd.ro; oana.amza@umfcd.ro
† This author contributed equally to the first author

ABSTRACT

Aim of the study: With chronic kidney disease (CKD) projected to be the fifth leading cause of death by 2040, this study investigates oral health and the relationship between salivary and renal function in pre-dialysis CKD patients. **Material and methods**: A cross-sectional survey of 51 pre-dialysis patients at a nephrology center in Bucharest collected socio-demographic data and assessed salivary function, oral health, and renal function. Measurements included saliva quality, pH, buffering capacity, calcium, phosphate, IL-6, TNF-α, and albumin, while oral health was evaluated using the DMFT index, OHI-S, GI, CAL, and assessments of periodontal disease. Renal function was assessed through serum creatinine, urea, and estimated glomerular filtration rate (eGFR). **Results**: Impaired saliva quantity was noted in 65% of participants (n=34), with elevated salivary calcium in 43.8% (n=22) and below-reference levels of IL-6 and TNF-α. Dental health was poor, reflected by a high DMFT score, fair oral hygiene, and moderate to severe gingival inflammation in 43.1% (n=22). Moderate or severe periodontal disease was observed in 45.1% (19.6% moderate, 25.5% severe), while median CAL and PD indicated moderate periodontal health. Renal function was compromised, with median eGFR placing 90.2% (n=46) in CKD stages 3–5. Significant associations included filled teeth and stimulated saliva ($p<0.01$), missing teeth and salivary calcium ($p<0.05$), filled teeth and IL-6 ($p<0.05$), and lower creatinine levels correlating with higher DMFT ($p<0.01$). **Conclusions**: This study underscores the significant link between pre-dialysis CKD and oral health, revealing higher prevalence of dental caries, periodontal disease, and salivary alterations in this group. Early intervention in oral health management is essential for improving outcomes and slowing disease progression.

Keywords: chronic kidney disease, oral health, salivary glands, renal function, periodontal disease, dental caries, xerostomia

1. INTRODUCTION

Chronic kidney disease (CKD) currently represents a serious public health issue, due to both its high and increasing prevalence [1], particularly because of the morbidity and mortality associated with it [2, 3], as being predicted to become the fifth leading cause of death by 2040 [4]. Additionally, it imposes significant costs on healthcare services, primarily through renal replacement therapies such as dialysis and kidney transplantation [5, 6]. Under these circumstances, scientific interest has shifted towards the pre-dialysis stages of CKD, focusing on strategies aimed at slowing disease progression and, consequently, delaying the initiation of replacement therapy. In this regard, the estimated glomerular filtration rate (eGFR) is commonly used as a measure for renal insufficiency in CKD patients during the pre-dialysis period [7].

DOI : 10.62610/RJOR.2024.4.16.6

Numerous studies [8, 9, 10, 11, 12] demonstrated that oral health is significantly compromised in patients with CKD, as evidenced by an increased prevalence of both dental caries and periodontal disease. Furthermore, periodontal disease appears to be involved in the pathogenesis of systemic inflammation in CKD [13], which influences morbidity and mortality [14, 15], particularly in relation to cardiovascular outcomes [16]. The extent to which improving oral health could slow the progression of CKD is a topic of considerable scientific interest [17, 18]. Additionally, patients with CKD exhibit a heightened susceptibility to infections [19], as both the disease itself and its treatment can lead to a range of systemic complications that pose a threat to oral health [20].

The growing interest in the relationship between oral and systemic health has led specialists to increasingly utilize the analysis of various characteristics and constituents of saliva for the diagnosis of systemic diseases and for monitoring general health, including renal function [21, 22]. Saliva testing offers several advantages over serum-based determinations, as saliva collection is a simple, non-invasive, and low-cost method with minimal risk of infection. Additionally, it can be performed by the patient without the need for assistance from healthcare personnel [23].

To date, the majority of studies examining the relationship between oral-dental status and CKD have focused on groups of patients undergoing dialysis [24, 25], with the pre-dialysis stage of the disease—critical from both a disease progression and cost-efficiency perspective—remaining largely under-investigated [26, 27]. Thus, the primary aim of the present research was to identify the prevalence and severity of oral-dental changes in patients with CKD in the pre-dialysis stage. Additionally, the study sought to establish the relationship between salivary function, oral health and renal function. Thus, the hypothesis of the current research was that patients with CKD in the pre-dialysis stage exhibit altered oral health status and impaired salivary function. It is anticipated that chronic renal impairment, due to its systemic effects, leads to changes in the oral cavity environment and modifies the composition and functional capacity of saliva.

2. MATERIAL AND METHODS

2.1. Study Design and Sampling Procedures

A cross-sectional study was conducted on individuals with CKD in the pre-dialysis stage, consecutively admitted to the Nephrology II Department of "Dr. Carol Davila" Clinical Hospital of Nephrology, Bucharest, between June 1, 2023, and September 30, 2023. Informed consent was obtained from all participants, which included detailed information regarding the study's objectives, duration, methods of data collection, and dissemination of results. Thus, all patients (n = 175) were invited to participate anonymously to the study. The study was conducted in accordance with the ethical principles outlined in the revised *Declaration of Human Rights* from the Helsinki Declaration, principles that are in line with the *Good Clinical Practice* guidelines and the applicable legal regulations.

2.2. *Study participants*

The inclusion criteria for participants in the study group encompassed a diagnosis of Chronic Kidney Disease (CKD) for at least one year and being in the predialysis stage (eGFR < 60 ml/min/1.73 m²). Additionally, participants needed to have the capacity to understand the study protocol and sign the informed consent. Conversely, the exclusion criteria included individuals who were completely edentulous, those undergoing

DOI : 10.62610/RJOR.2024.4.16.6

immunosuppressive therapy, individuals with neuro-psychiatric disorders, or malignant conditions, as well as pregnant or breastfeeding women. Thus, out of the initial cohort (n=175), 44 patients declined to participate, 38 were involved in other clinical studies, respectively 23 were excluded because of being edentulous. Initially, 93 patients agreed to undergo the dental examination; however, 19 of them gave up during the examination, and consequently, 51 participants remained for analysis.

2.3. Data Collection

Four main categories of data were collected, namely socio-demographic and habitual data, salivary function data, oral status, and renal function of the participants. The socio-demographic and habitual data were obtained from the hospital medical records, including participants' age, sex, place of residence (urban/rural), and educational level.

For salivary assessments, the GC Saliva-Check Buffer kit (GC Corporate, Tokyo, Japan), an in vitro test for evaluating the quality, pH, and buffering capacity of saliva, was used in the first phase. Each participant was instructed to refrain from smoking, consuming solids or liquids, and performing oral hygiene for at least one hour prior to sample collection. Stimulated saliva samples were collected in the morning to avoid circadian variations [28]. Participants placed in the supine position were instructed to relax during saliva collection. For pre-stimulation, they were asked to chew a paraffin cube (approximately 1g) from the kit for 60 seconds and swallow the saliva produced. Following this, they were instructed to expectorate saliva into sterile containers every minute for a total of 5 minutes. The entire volume of saliva collected during this period was measured using the milliliter gradations on the collection container. The volume of stimulated saliva was categorized as very low (< 3.5 ml), low (3.5-5 ml), or normal (> 5 ml). The buffering capacity of saliva using the kit's colorimetric tests was classified into four categories: normal/high, low, or very low. Additionally, salivary pH was evaluated using the kit's test strip by moistening it with a drop of saliva for 10 seconds. The resulting color change was then compared to the provided color chart, and the corresponding pH value was recorded.

The remaining saliva samples were subsequently used for laboratory tests. Approximately 2 ml of the total saliva collected per participant was immediately centrifuged at 3000 rpm for 10 minutes to remove cellular debris. The supernatant was stored in small aliquots at -80°C for further analysis. The biochemical analyses of saliva focused on the following parameters:

- Antioxidant capacity of saliva**:** Parameters describing the antioxidant capacity of saliva, including total antioxidant capacity, and glutathione peroxidase, were measured immediately after sample collection using analysis kits from Biosystems (Barcelona, Spain) and Randox (London, UK) on an automated analyzer (Biosystems, Barcelona, Spain).

- Concentration of calcium and phosphate ions in saliva:
The concentration of calcium ions was determined using the Arsenazo reagent method (Biosystems, Spain) adapted to an automated biochemical analyzer (A15; Biosystems, Spain), while the concentration of phosphate ions was measured using the ammonium molybdate method (Biosystems, Spain) also adapted to an A15 automated biochemical analyzer (Biosystems, Spain).

- Concentration of inflammation biomarkers:
The concentrations of IL-6, TNF-α, and albumin in saliva were determined through chemiluminescence using an automated

DOI : 10.62610/RJOR.2024.4.16.6

Immulite analyzer (Siemens, USA). The reagents were provided by Siemens, USA.

The results of the laboratory analyses were expressed by normalizing the concentration of each parameter to the salivary albumin concentration, in order to account for variations in salivary flow rate.

The evaluation of oral health status was performed through direct clinical examination by a single dentist, in accordance with the World Health Organization (WHO) guidelines [29]. For this purpose, a minimal set of instruments was used, consisting of a mirror, dental probe, and periodontal probe. The oral status of each participant was determined by calculating the DMFT index (decayed–missing–filled teeth), a numerical indicator used to assess the prevalence of dental caries, which remains a widely used metric for evaluating oral health status [30]. This index applies to the permanent dentition and is expressed by the total number of teeth (or surfaces) that are decayed (D), missing (M), or filled (F). In the present study, DMFT scores ranged from 0 to 28, as the third molar was excluded from the assessment. In cases where a carious lesion was present, or when a carious lesion coexisted with a crown restoration, the tooth was recorded as decayed (D). Similarly, the presence of either a temporary or permanent filling, in the absence of a carious lesion, was recorded as filled (F). Teeth restored for reasons other than dental caries (e.g., trauma, hypoplasia, abutment teeth, or dental sealants) were also categorized as filled (F). The DMFT index was calculated by summing the number of decayed, missing, and filled teeth (DMFT = D + M + F). For the study group, the mean DMFT score was calculated by summing all the individual scores and then dividing the total by the number of examined individuals.

Periodontal status was evaluated through inspection and palpation of the superficial and deep marginal periodontium, using exploratory probes and a periodontal probe. The assessment included observation of the interdental papillae, free gingival margin, and attached gingiva, focusing on changes in colour, texture, consistency, adherence to underlying tissues, gingival attachment level, detection of tooth mobility, and measurement of periodontal pocket depth. Three periodontal indices were evaluated, the Simplified Oral Hygiene Index (OHI-S), the Gingival Index (GI), the Clinical Attachment Level (CAL). Ffinally, tooth mobility was registered.

- OHI-S [31] consists of two components: the Simplified Debris Index (DI-S) and the Simplified Calculus Index (CI-S). The DI-S is scored as follows: 0 = no plaque; 1 = supragingival plaque in the cervical third; 2 = supragingival plaque in the middle third; 3 = plaque in the incisal or occlusal third. The CI-S is scored as follows: 0 = no calculus; 1 = supragingival calculus in the cervical third; 2 = supragingival calculus in the middle third; 3 = calculus in the incisal or occlusal third. Both indices provide a numerical representation of the amount of plaque/calculus on six predetermined surfaces: the buccal surfaces of the maxillary first molars, the lingual surfaces of the mandibular first molars, and the buccal surfaces of the upper right and lower left central incisors.

- GI [32, 33] was used to record qualitative changes in the gingiva, scored as follows: 0 = clinically normal gingiva; 1 = mild inflammation – slight change in colour, slight edema, no bleeding on probing; 2 = moderate inflammation – congestion, edema, bleeding on probing; 3 = severe inflammation – marked edema, stasis, ulcerations with a tendency for spontaneous bleeding. Bleeding was assessed by gentle probing along the walls of the gingival sulcus. The scores for the four dental surfaces were summed and divided by four to determine the GI for each

DOI : 10.62610/RJOR.2024.4.16.6

respective tooth. The final GI was calculated by summing the values for each tooth and subsequently dividing by the number of examined teeth, thereby expressing the severity of gingivitis for the respective subject [33] (0.1-1.0 = mild inflammation; 1.1-2.0 = moderate inflammation; 2.1-3.0 = severe inflammation).

- CAL was calculated by summing the values of two measurements: the probing depth (PD) and the level of the gingival margin. The PD was determined by measuring the distance from the gingival margin to the base of the periodontal sulcus/pocket using a periodontal probe. The level of the gingival margin was also measured with the periodontal probe, calculating the distance in millimeters from the level of the gingival margin to the cementoenamel junction (in an apical direction indicating gingival recession, or in a coronal direction depending on the present situation), at six specific locations for each tooth. The obtained values were rounded to the nearest whole number. For each tooth, the maximum CAL value was used.

Dental mobility was assessed both horizontally and vertically using the handles of the dental probe and the dental mirror. Pathological dental mobility was categorized into one of the following degrees of mobility: Grade I – mobility of the incisal or occlusal edge in the transverse plane of 1 mm; Grade II – mobility of the incisal or occlusal edge in the transverse plane of more than 1 mm; Grade III - when the tooth is mobile in the axial plane.

The subjects were categorized into four stages based on Clinical Attachment Level (CAL) and probing depth (PD), following criteria from the Centers for Disease Control and Prevention and the American Academy of Periodontology [34]. Stage I indicates no periodontal disease, with no signs of mild, moderate, or severe marginal periodontitis. Stage II represents early marginal periodontitis, characterized by two or more sites with proximal gingival attachment loss of three millimeters or more and either two interproximal sites with probing depths of four millimeters or more (not on the same tooth) or one interproximal site with a probing depth of five millimeters or more. Stage III signifies moderate marginal periodontitis, with criteria identical to Stage II. Finally, Stage IV indicates severe marginal periodontitis, defined by two or more sites with proximal gingival attachment loss of six millimeters or more and at least one interproximal site with a probing depth of five millimeters or more.

Renal function determinations for the participants included routine blood tests for CKD conducted at the hospital where they were admitted. The serum creatinine and urea values obtained from these tests were retained for the study, along with the estimated glomerular filtration rate (eGFR). The eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) formula [35], which incorporates four variables:

eGFR=175×(serum creatinine in mg/dL)−1.154×(age)−0.203×0.742(if female)×1.212(for AfricanAmericans).

Based on the eGFR values and following the K/DOQI guidelines, the subjects were classified into various stages of chronic kidney disease. Stage 0 indicated an eGFR of 90 mL/min/1.73 m^2 or higher, signifying no signs of kidney damage but the presence of risk factors for CKD. Stage 1 was characterized by kidney damage with a normal or increased glomerular filtration rate (eGFR $\geq$ 90 mL/min/1.73 m^2). Stage 2 represented kidney damage with mildly decreased glomerular filtration, with an eGFR between 60 and 89 mL/min/1.73 m^2. Stage 3 indicated moderately decreased glomerular

DOI : 10.62610/RJOR.2024.4.16.6

filtration, with an eGFR ranging from 30 to 59 mL/min/1.73 m². Stage 4 was marked by severely decreased glomerular filtration, with an eGFR between 15 and 29 mL/min/1.73 m². Finally, Stage 5 indicated kidney failure, characterized by an eGFR of less than 15 mL/min/1.73 m² or the necessity for renal replacement therapy.

2.4. Data analysis

Statistical analysis was performed using SPSS version 20. Both normally distributed and non-parametric data were uniformly presented as the median and the 95% confidence interval. Bivariate correlation analysis was used to test statistical correlations between variables. The Pearson correlation coefficient assessed the validity of these correlations. A Pearson coefficient close to 1, whether positive or negative, indicates a strong and statistically significant correlation. A negative Pearson coefficient signifies an inverse correlation, while a positive coefficient indicates a direct correlation. The significance level was set at 5%, with a 95% confidence interval.

3. RESULTS AND DISCUSSIONS

The study included 51 pre-dialyzed CKD subjects (19 males, 32 females), with a median age of 58 years (50.41–59.28; range 18–85), evaluated between June 1, 2023, and September 30, 2023. Depending on their place of residence, 27.45% (n=14) lived in rural areas, while the remaining 72.55% (n=37) lived in urban areas. The analysis of the education level showed that 57% (n=29) of the participants had secondary education, 23% had completed elementary school (n=12), and the remaining 20% (n=10) had higher education.

Regarding salivary function assessed with the GC kit (Table 1), stimulated saliva quantity was normal (> 5 mL) in 35% (n=18) of participants, low (3.5–5 mL) in 37% (n=19), and very low (< 3.5 mL) in 28% (n=14). The median stimulated saliva volume was 5 (4.29–5.54) mL. Salivary buffering capacity was normal in 96.1% (n=49) of patients; only 3.9% (n=2) had low buffering capacity. Salivary pH was within normal limits (6.8–7.8) for 94% (n=48) of subjects, while moderately acidic pH (6–6.6) was recorded in 6% (n=3). The median pH for the studied group was 7.6 (7.31–7.50).

Table 1. Salivary function of investigated pre-dialysed CKD subjects assessed by the Saliva Check Buffer Kit (GC)

Properties	Median Values
Stimulated saliva quantity	5(4,29-5,54) mL
Salivary buffering capacity (%):	
- normal	96.1
- low	3.9
Salivary pH (%):	7,6(7,31-7,50)
- normal	94
- moderately acid	6

Regarding salivary function assessed through biochemical tests (Table 2), oxidative stress was evaluated by analyzing total antioxidant capacity and glutathione peroxidase in saliva. The median values recorded were: 1.03 (1.01–1.09) mg/mg albumine for glutathione peroxidase; 0.89 (0.87–0.93) mg/mg albumine for total antioxidant capacity; and 19.30 (19.23–20.18) U/mg albumine for glutathione peroxidase. Calcium ion concentration was above the reference range (1.19–2.78 mg/mg albumin) in 43.8% (n=22) of cases and normal in 56.2% (n=29). The median value was 2.70 (2.60–2.80) mg/mg albumine. Phosphate ion levels were within the reference range (0.475–4.47 mmol/mg albumin) for all participants, with a median value of 3 (−797–2469.86) mmol/mg albumine. The inflammatory markers TNF-α

DOI : 10.62610/RJOR.2024.4.16.6

and IL-6 in saliva had median values of 0.03 (0.04–0.07) pg/mg albumin and 0.08 (0.09–0.14) pg/mg albumin, respectively (Tab. 3). IL-6 was below the normal range, which is indicated as 0.09 to 0.14 pg/mg, same for the salivary TNF-α, given as 0.03 (0.04–0.07) pg/mg albumin, below the normal range, which is 0.04 to 0.07 pg/mg.

Table 2. Salivary biomarker profiles of investigated pre-dialysed CKD subjects

Properties	Median Value
Total antioxidant capacity	0,89(0,87-0,93) mg/mg albumin
Glutathione peroxidase	19,30(19,23-20,18) U/mg albumin
Calcium ion concentration	2,70(2,60-2,80) mg/mg albumin
- normal	56.2
- increased	43,8
Phosphate ion concentration	3(-797-2469,86) mmol/mg albumin
TNF α	0,03(0,04-0,07) pg/mg albumin
IL-6	0,08(0,09-0,14) pg/mg albumin

Following the evaluation of dental status (Table 3), the DMFT index recorded a value of 16 (13.77–17.83), with a median value of 3 (2.55–4.14) for teeth with carious lesions, 3 (2.85–4.99) for teeth with crowns, and 6 (6.56–10.49) for missing teeth. The average OHI-S value was 1.75 (1.72–2.26), the DI-S was 1 (0.95–1.23), and the CI-S was 0.80 (0.74–1.05). According to OHI-S values, 27.45% (n=14) of cases had good oral hygiene, 64.71% (n=33) had moderate oral hygiene, and 7.84% (n=4) had poor oral hygiene. The evaluation of GI severity in the group indicated that the majority, 56.9% (n=29), had mild gingival inflammation, 29.4% (n=15) had moderate gingival inflammation, and the remaining 13.7% (n=7) had severe gingival inflammation.

For the evaluation of periodontal status, the aforementioned classification was considered, showing that 29.45% of participants had no periodontal disease, 25.5% had early periodontal disease, 19.6% had moderate periodontal disease, and 25.5% had severe periodontal disease. The median values obtained for CAL and PD in the studied group were 3 (3.14–3.35) and 3 (2.71–2.87), respectively. Regarding dental mobility of the teeth present in the subjects' dental arches, of the 1,013 teeth analyzed, 82.7% showed no mobility, 11% showed Grade I mobility, 4.9% showed Grade II mobility, and 1.4% showed Grade III mobility.

Table 3. Oral health of pre-dialysed CKD subjects

Parameter	Median Values
DMFT	16(13,77-17,83)
- D	3(2,55-4,14)
- M	6(6,56-10,49)
- F	3(2,85-4,99)
OHI-S	1,75(1,72-2,26)
- good (%):	27.45
- moderate(%)	64.71
- poor (%)	7 .84
DI-S	1(0,95-1,23)
CI-S	0,80(0,74-1,05)
- normal (%):	56.2
- increased (%):	43.8
GI%,	
- mild	56.9
- moderate	29.4
- severe	13.7
Periodontal disease(%)	
- absence	29.5
- incipient	25.5

DOI : 10.62610/RJOR.2024.4.16.6

- moderate	19.6
- severe	25.5
CAL	3(3,14-3,35)
PD	3(2.71-2.87).
Dental mobility(%)	
- absence	82.7
- grade I	11
- grade II	4.9
- grade III	1.4

Renal function was assessed by median eGFR values of 29.81 (28.15–38.39) ml/min/1.73 m², with a minimum of 4 ml/min/1.73 m² and a maximum of 77 ml/min/1.73 m². The median values of renal function indicators are presented in Table 4. Based on the level of eGFR, patients were classified into stages of chronic kidney disease according to the guidelines: 9.8% (n=5) of cases were classified as stage 2 CKD, 39.2% (n=20) as stage 3 CKD, 35.3% (n=18) as stage 4 CKD, and 15.7% (n=8) as stage 5 CKD.

Table 4. Renal function of investigated pre-dialysed CKD subjects

Parameter	**Median value**
Creatinine (mg/dL)	1,80(1,97-3,55)
eGFR (ml/min/1,73m^2)	29,81(28,15-38,39)
Urea (mg/dL)	68(71,01-104,61)

Through bivariate analysis, associations and causal between salivary function and oral health, as expressed by the DMFT index, were tested. Thus, a single significant association was identified, namely between the high number of filled teeth and the reduced amount of stimulated saliva (Table 5).

Table 5. Dental health and salivary function evaluated by the Check Buffer kit in pre-dialysed CKD subjects

	Salivary pH	**Stimulated saliva quantity**	**Buffer capacity**
Decayed			
Pearson Correlation	085	-.035	-.151
Sig.(2-tailed)	.552	.806	.391
N	51	51	51
Missed			
Pearson Correlation	.045	- .055	.058
Sig.(2-tailed)	.753	.704	.686
N	51	51	51
Filled			
Pearson Correlation	.098	.463*	.158
Sig.(2-tailed)	.495	.001	.267
N	51	51	51

*p< 0,01

As for the biomarker profiles of saliva, statistically significant associations were identified between the number of

DOI : 10.62610/RJOR.2024.4.16.6

edentulous teeth and the amount of salivary calcium on one hand, and between the number of filled teeth and IL-6 concentrations in saliva on the other hand (Table 6).

Table 6. Dental health and salivary biomarkers of pre-dialysed CKD subjects

	TAC	GPX	Salivary calcium	Salivary phosphate	IL-6	TNFα
Decayed						
Pearson	-.114	-.081	- .125	.219	-.217	.107
Correlation	.440	.583	.396	.136	.138	.467
Sig.(2-tailed)	48	48	48	48	48	48
N						
Missed						
Pearson	.246	-.203	.326*	-.087	.163	.247
Correlation	.092	.165	.024	.556	.270	.090
Sig.(2-tailed)	48	48	48	48	48	48
N						
Filled						
Pearson	-.156	.053	.060	-.061	.306*	.200
Correlation	.288	.719	.685	.682	.034	.173
Sig.(2-tailed)	48	48	48	48	48	48
N						

*p< 0,05

Assesing the correlations between oral status and renal function, lower creatinine levels were associated with higher DMFT index values (Table 7).

Table 7. Oral health and renal function of pre-dialysed CKD subjects

	Serum creatinine	eGFR	Serum Urea	CKD stage
DMFT Index				
Pearson Correlation	-.427*	.149	.044	-.223
Sig.(2-tailed)	.002	.301	.768	.119
N	50	50	47	50
DI-S				
Pearson Correlation	-.086	.108	.201	.025
Sig.(2-tailed)	.553	.454	.175	.865
N	50	50	47	50
CI-S				
Pearson Correlation	.097	-.033	.208	.119
Sig.(2-tailed)	.504	.821	.161	.411
N	50	50	47	50
OHI-S				
Pearson Correlation	.013	.036	.222	.081
Sig.(2-tailed)	.931	.806	.134	.574
N	50	50	47	50
GI				.
Pearson Correlation	-.017	.062	.178	.003
Sig.(2-tailed)	.908	.667	.230	..984

DOI : 10.62610/RJOR.2024.4.16.6

N	50	50	47	50
CAL Pearson Correlation Sig.(2-tailed) N		 001 .985 994		 -.014 .654 994
PD Pearson Correlation Sig.(2-tailed) N		 -.0.11 7.38 994		 -.0.15 647 994
Dental Mobility Pearson Correlation Sig.(2-tailed) N		 -.007 .834 1013		 -.061 .055 988
Periodontal disease stage Pearson Correlation Sig.(2-tailed) N		 -.032 .827 50		 .005 .972 50

* $p < 0.01$

4. DISCCUSSION

CKD is a syndrome characterized by the progressive deterioration of renal function. Active intervention in comorbidities may be associated with a slowdown in the rate of renal function decline, thereby postponing the need for renal replacement therapy, such as dialysis or transplantation (the so-called 'kidney death'). CKD is often associated with high prevalences of malnutrition, inflammation, and atherosclerosis, which contribute to increased morbidity and mortality [36]. Oral conditions, often asymptomatic, can lead to tooth loss, primarily through complications related to dental caries but also through periodontal involvement, significantly impacting the nutritional status and inflammation in these patients, which adversely affects prognosis [37, 38].

The present study aimed to explore the correlation between oral health and pre-dialysis patients with CKD. In the early stages of CKD, patients with poor oral health, if identified and treated, may benefit from a slower progression of kidney disease and a reduction in comorbidities [39]. The average age of the patients was 55 years, which is still lower than the European average reported in the annual registry of the ERA-EDTA (European Renal Association-European Dialysis and Transplant Association) for patients starting dialysis, which is 65 years [40]. The majority of the study participants were female, despite the higher prevalence of chronic kidney disease (CKD) typically reported among males [41]. This discrepancy may be attributed to a greater interest in oral health among women, as well as their higher propensity to participate in clinical trials [41]. Such findings align with broader evidence suggesting that women are often more engaged in health-related activities and clinical research [42], reflecting their higher awareness and involvement in preventive care measures. Moreover, in the context of preventive care, educational attainment plays a critical role, particularly in determining the likelihood of seeking medical consultation and adhering to prescribed treatments. In this cohort, only 20% of patients had completed higher education, while 57% had attained secondary education, highlighting the

DOI : 10.62610/RJOR.2024.4.16.6

potential influence of educational background on healthcare engagement. Preventive and educational programs focused on oral health have a positive impact on the population; however, their effectiveness is contingent upon the levels achieved in individuals' professional trajectories. The lower percentage of patients from rural areas participating in this study may be attributed to their limited engagement with healthcare providers, which is often compounded by lower educational and informational levels regarding health [43]. Furthermore, this demographic may face greater challenges in accessing tertiary care facilities, potentially hindering their health-seeking behaviour and overall health outcomes.

An essential part of our research focused on salivary investigations, particularly due to the limited number of publications in pre-dialysis CKD patients. Various studies have suggested that salivary flow decreases in patients with CKD, reaching levels below the threshold for hyposalivation. This reduction has been hypothesized to be linked to direct glandular impairment and/or fluid restriction often advised for CKD patients, as reported by other researchers [44]. Our study observed predominantly low stimulated salivary secretion in pre-dialysis patients (65%), a finding that may also explain the high prevalence of dental caries in this population subset.

Salivary pH elevations are frequently observed in patients with CKD [45]. However, in the present study, salivary pH levels and salivary buffering capacity remained within normal limits for the majority of subjects (94% and 96.1%, respectively), presenting a divergent result. Additionally, the majority of CKD cases in our study exhibited reduced stimulated saliva production, likely due to inflammatory processes within the glandular parenchyma. Similar findings were reported by Thorman et al. [17], though different results were noted by Sobrado Marinho et al. [46] and Bayraktar et al. [47].

As a consequence of impaired renal function, CKD patients may experience associated inflammatory diseases such as amyloidosis, rheumatoid arthritis, and Sjogren's syndrome, where inflammatory markers like IL-6 and TNF–α are used to assess inflammatory status. Elevated levels of these cytokines indicate an increased risk of endothelial cell damage and the development of chronic cardiovascular diseases [48]. In our analysis, we observed a strong correlation between the DMFT index and TNF–α level, suggesting ongoing chronic inflammatory processes. Oral diseases, including caries, marginal periodontitis, and chronic apical periodontitis, are also chronic inflammatory processes, thus explaining the significant association between higher DMFT values and increased TNF–α levels in CKD patients.

Patients with CKD exhibit a higher morbidity and mortality rate due to cardiovascular causes, which cannot be fully explained by traditional cardiovascular risk factors [49]. Consequently, recent research has emphasized oxidative stress as a novel risk factor [50]. The generation of pro-oxidant compounds plays a physiologically significant role as an essential phase in inflammation and tissue repair processes. However, inappropriate or chronic activation of oxidative processes, as seen in pathological conditions like uremia, may contribute to tissue and cellular damage in individuals with CKD) the balance between pro-oxidant and antioxidant capacities is tipped toward increased oxidative stress. This imbalance begins in the early stages of CKD, becoming most pronounced in patients undergoing dialysis. In this study was found that the

DOI : 10.62610/RJOR.2024.4.16.6

salivary oxidative stress parameters among the CKD patients examined were lower than those recorded in the non-CKD population. This finding contrasts with the results of Bibi et al. [51], who reported higher stress parameters in a cohort of pre-dialysis or peritoneally dialyzed patients. However, in terms of salivary electrolyte levels, the stimulated salivary calcium concentration in 43.8% of the patients exceeded the normal reference range. Furthermore, the relationship between estimated glomerular filtration rate (eGFR) and inflammatory biomarkers remains a topic of ongoing scientific debate. Studies suggest that elevated levels of inflammatory markers, such as C-reactive protein (CRP) and interleukin-6 (IL-6), may be present even in the early stages of kidney disease [52]. This evidence highlights a multifaceted interaction between oxidative stress, inflammation, and electrolyte imbalances in CKD, suggesting a need for further research into their roles in disease progression and patient outcomes.

Additionally, the level of the immunological marker IL-6 tends to be higher in patients with poor dental health compared to those with fewer dental issues [53]. In our study, elevated IL-6 levels were significantly associated with a higher number of restored teeth, a finding similar to those reported by Al-Wahadni and Al-Omari [54] as well as Bots et al. [25]. It can be argued that beneath older, extensive restorations, the dental pulp undergoes a slow necrotic process, leading to pulp death and gangrene. The infiltration and proliferation of microorganisms within the root canals cause apical periodontitis, initiating the immune response and activating complement factors. Failure to treat these conditions promptly can lead to chronic inflammation, elevating pro-inflammatory cytokines (IL-6, CRP, and TNF–α).

It is widely recognized that patients with CKD frequently exhibit significant oral health issues, including xerostomia, uremic halitosis, and alterations in taste and salivary secretion [55]. Moreover, a higher prevalence of dental caries, gingivitis, tooth mobility, and multiple edentulous areas has been reported in this population [56]. According to the data presented in this research, oral health status appears to be poorer in even in pre-dialysis patients with CKD compared to the general population when considering indicators of dental health and periodontal disease. Thus, patients with CKD exhibited an alarming DMFT index, nearly double that of the general population, specifically 16, compared to 8.4, as indicated by the most recent data from the World Health Organization (WHO) [57]. Our findings were influenced by the higher number of edentulous areas compared to decayed and extracted teeth. Analyzing convergent results, Atassi et al. [58] suggested that these factors may not be directly linked to CKD but rather associated with the socioeconomic status of the patient and their limited access to preventive and curative dental treatment. Consequently, patients typically consult a dentist only when experiencing pain, with tooth extraction being the preferred procedure in such cases. This assertion, however, also applies to the general population and does not adequately explain the observed differences in oral health status between pre-dialysis patients with CKD and the general population. In our study, a higher number of teeth with coronal restorations associated with increased stimulated saliva production. Interestingly, patients who are more proactive in managing their general health and attend regular check-ups with both nephrologists and dentist exhibit treated carious lesions and adequate control of renal function. This attention to preventive care is also associated with fewer complications

DOI : 10.62610/RJOR.2024.4.16.6

affecting the salivary glands, such as xerostomia.

Furthermore, the findings of this study align with those presented by Bayraktar et al. [47] in dialysis patients, who reported a relationship between educational level and oral health status among these individuals. Specifically, the DMFT and DI-S indices were significantly lower in the group of peritoneal dialysis patients compared to their hemodialysis counterparts, with the former group containing five times as many individuals with higher education. In the cases we investigated, a moderate state of oral hygiene was observed, which may also be a consequence of the patients' educational levels. This situation correlates significantly with an increased number of dental caries as well as the presence of dental restorations. A potential explanation for this phenomenon could be the level of health education, as a substantial majority of patients in the studied cohort had completed only secondary (57%) or elementary (23%) education. Moreover, several studies [58, 59, 60] have indicated poor oral hygiene among patients with CKD. The level of oral hygiene may be influenced by the manifestations of CKD itself. Patients tend to prioritize their chronic kidney condition, often neglecting preventive measures for dental health issues, as noted by Souza et al. [61].

Previous studies by Atassi et al. and Bayraktar et al. highlighted that CKD patients exhibit a significantly higher prevalence of edentulous areas, potentially reflecting a state of lower systemic inflammation [62, 63]. This aligns with our findings suggesting that reduced creatinine levels in CKD may correspond with increased missing teeth, potentially due to factors like immune suppression and inadequate oral care. For instance, it has been established that patients with CKD are more susceptible to oral health issues such as xerostomia, periodontal disease, and gingival inflammation, often due to metabolic disturbances and medication side effects. These symptoms can lead to a higher prevalence of edentulism, which in turn correlates with lower systemic inflammation markers, including reduced serum creatinine levels.

Various studies indicated that oral hygiene in hemodialysis patients is substantially poorer than in the general population [59, 60], a condition attributed to the chronic nature of their illness. As a result, patients are primarily focused on managing their systemic disease, often neglecting preventive care for other aspects of their health. This neglect is further compounded by psychological implications; patients frequently experience stress due to dietary restrictions and medication regimens, contributing to anxiety and depression [64]. In our study, plaque and tartar indices reflected oral hygiene status, with values of 1 or below observed in most patients, aligning with the significant proportion (64.4%) who demonstrated only moderate oral hygiene. Our findings even recorded lower values compared to hemodialysis patients, who tend to accumulate tartar more rapidly and in greater quantities, likely due to elevated calcium and phosphate levels in their saliva [65]. Furthermore, the subjects demonstrated a 100% prevalence of gingival inflammation across various severity levels, a particularly significant observation that is consistent with other findings [54, 59, 66] from studies involving dialysis patient cohorts. This result indicates that gingival inflammation arises in the early stages of CKD and persists throughout the disease course, from the pre-dialysis phase to the stage where renal replacement therapy becomes necessary.

Moreover, there is evidence suggesting that periodontal disease may serve

DOI : 10.62610/RJOR.2024.4.16.6

as a hidden source of systemic inflammation in patients with CKD and could, in fact, predict the development of end-stage chronic kidney disease and nephropathy in diabetic patients [67, 68]. However, to date, there are relatively few studies addressing the prevalence of periodontal disease among pre-dialysis CKD patients. This study revealed that periodontal disease was present in 70.6% of pre-dialysis patients, a higher prevalence than that observed in the general population (47.2%) [69]. Furthermore, severe periodontal disease was identified in 25.5% of these patients, a figure surpassing that reported by the WHO in 2022 for the general population [70].

Patients with periodontal disease exhibit high local production of pro-inflammatory cytokines that can enter the bloodstream, as evidenced by elevated levels of inflammatory markers in both gingival tissues and serum [71]. Thus, periodontitis may exert systemic effects that disrupt homeostasis and negatively impact existing systemic diseases. The present study identified statistically significant associations between probing depth (PD) and clinical attachment level—parameters used to assess periodontal disease prevalence—and TNFα levels in saliva, likely due to periodontal inflammation. One key research published in 2024 describes how cytokines like tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) drive systemic inflammation, exacerbating the progression of cardiovascular disease in CKD through pathways associated with oxidative stress and metabolic imbalance [72]. Considering that periodontal disease may influence CKD progression through inflammatory mechanisms, and that CKD has established effects on the severity of periodontal disease, the bidirectional relationship between these two conditions warrants ongoing clinical attention.

The limitations of this study include its cross-sectional design, which, on one hand, restricts the ability to establish causal relationships, and the relatively small number of eligible participants on the other. Additionally, the absence of a control group poses challenges in drawing definitive conclusions. Furthermore, the unicentric nature of the study presents another limitation, as there may be differences in the demographic characteristics of patients attending a nephrology center compared to the broader population of individuals with CKD in Romania. In the context of oral health and salivary factors in pre-dialysis CKD patients, it is essential to consider these limitations when interpreting the findings. The analysis of oxidative stress and inflammatory cytokines was limited to saliva, although a comprehensive understanding of their influences on CKD would have benefited from serum analysis as well, allowing for subsequent comparison of results.

Given that patients with CKD often experience altered salivary parameters and increased oxidative stress, as established in previous research, it is crucial to explore how these factors interact with oral health. The increased oxidative stress observed in CKD patients may exacerbate oral health issues, potentially leading to a higher incidence of periodontal disease and other oral complications. Moreover, understanding the balance between pro-oxidant and antioxidant capacities in saliva could provide valuable insights into the overall health status of CKD patients. Thus, the identified limitations underscore the need for further research that includes larger, multicentric studies and comprehensive analyses of both salivary and serum biomarkers. This approach would

DOI : 10.62610/RJOR.2024.4.16.6

enhance our understanding of the interplay between oxidative stress, inflammation, and oral health in this vulnerable population, ultimately guiding more effective management strategies.

CONCLUSIONS

CKD is intricately linked to oral health, with pre-dialysis patients demonstrating a markedly higher prevalence of dental caries, periodontal disease, and xerostomia compared to the general population. Addressing oral health issues early in CKD management can contribute to slowing disease progression and reducing related comorbidities. This underscores the importance of integrated healthcare strategies that encompass both renal and oral health to enhance overall patient outcomes. Moreover, education on oral hygiene habits plays a crucial role in improving health outcomes among CKD patients. Increasing awareness and knowledge about preventive dental care empowers individuals to take proactive steps in managing their oral health, which can positively influence their overall well-being.

The relationship between oral health and systemic inflammation is also significant. Poor oral health is associated with elevated levels of inflammatory cytokines in CKD patients, indicating that oral conditions may exacerbate systemic inflammation and negatively impact renal health. Additionally, the findings regarding salivary oxidative stress underscore the intricate interplay between oxidative stress and inflammation in CKD, which further influences patient health. The relationship between periodontal disease and CKD suggests a bidirectional influence, where each condition may exacerbate the other through inflammatory pathways. High levels of pro-inflammatory cytokines associated with periodontal disease can contribute to systemic inflammation, potentially worsening CKD progression. Conversely, the presence of CKD can intensify the severity of periodontal disease. Recognizing and addressing these interconnected health issues is essential for improving patient management and outcomes, highlighting the need for a comprehensive approach to healthcare that considers both renal and oral health.

REFERENCES

1. Zhang Q-L; Rothenbacher D. Prevalence of chronic kidney disease in population-based studies: systematic review. *BMC public health*, 2008, 8.1: 117.
2. Keith DS, Nichols GA, Gullion CM, Brown JB., Smith DH. Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. *Archives of internal medicine*, 2004; *164*(6), 659-663.
3. Vanholder R, Massy Z, Argiles A, Spasovski G, Verbeke F, Lameire N. Chronic kidney disease as cause of cardiovascular morbidity and mortality. *Nephrology Dialysis Transplantation*, 2005; *20*(6), 1048-1056.
4. Ruperto, M.; Barril, G. Nutritional Status, Body Composition, and Inflammation Profile in Older Patients with Advanced Chronic Kidney Disease Stage 4–5: A Case-Control Study. *Nutrients* 2022, 14, 3650. https://doi.org/10.3390/nu14173650.
5. Blotiere P O, Tuppin P, Weill A, Ricordeau P, Allemand H. The cost of dialysis and kidney transplantation in France in 2007, impact of an increase of peritoneal dialysis and transplantation. *Nephrologie & therapeutique*, 2010; *6*(4), 240-247.

DOI : 10.62610/RJOR.2024.4.16.6

6. Rocha M J, Ferreira S, Martins L S, Almeida M, Dias L, Pedroso S, Henriques A C, Almeida R, Cabrita A. Cost analysis of renal replacement therapy by transplant in a system of bundled payment of dialysis. *Clinical transplantation*, 2012; *26*(4), 529-531.
7. Janmaat CJ, van Diepen M, van Hagen CC, Rotmans JI, Dekker FW, Dekkers OM. Decline of kidney function during the pre-dialysis period in chronic kidney disease patients: a systematic review and meta-analysis. *Clin Epidemiol.* 2018 May 25;10:613-622.
8. Kossioni, A.E.; Chatzopoulou, S.A. The Oral Health of Patients with Chronic Kidney Disease: A Review of the Literature. *Nutrients* 2020, 12, 3168.
9. Aroca, S.; Matesanz, M.; Hernández, J.L.; Lobo, C.; López, J.; Rodríguez, C.; Aguirre, J.J.; Sanz, M. The Effect of Periodontal Therapy on the Inflammatory Profile in Patients with Chronic Kidney Disease. *Nutrients* 2021, 13, 2163. https://doi.org/10.3390/nu13072163.
10. Yalçın, S.; Çelik, E.; Altuntaş, S.H. The Impact of Chronic Kidney Disease on Oral Health-Related Quality of Life. *Nutrients* 2022, 14, 5722. https://doi.org/10.3390/nu14125722.
11. Kamal, A.; Awan, M.U.; Hussain, A.; Tareen, A.; Sadaqat, M.; Faryal, R.; Majeed, A.; Bukhari, S.A.C.; Sheikh, A.B.; Hussain, Z. Oral Health Status in Patients with Chronic Kidney Disease: A Cross-Sectional Study. *BMC Nephrology* 2021, 22, 149. https://doi.org/10.1186/s12882-021-02153-2.
12. Mardini, H. The Association between Chronic Kidney Disease and Oral Health: A Systematic Review and Meta-Analysis. *BMC Oral Health* 2023, 23, 109. https://doi.org/10.1186/s12903-023-02266-3).
13. Beck JD, Offenbacher S, Williams R, Gibbs P, Garcia R: Periodontitis: A risk factor for coronary heart disease? *Ann Periodontol* 1998; 3:127–141.
14. Hwang, Y.J.; Kwon, H.C.; Lee, S.W.; Kim, Y.D.; Moon, Y.J.; Kim, Y.J.; Kim, D.H. Association between Periodontal Disease and Chronic Kidney Disease: A Systematic Review and Meta-Analysis. *Nutrients* 2021, 13, 2644. https://doi.org/10.3390/nu13082644.
15. Furuya, Y.; Tomiyama, C.; Fujita, Y.; Matsumoto, S.; Yamamoto, T.; Nakano, K.; Yamamoto, M. Influence of Periodontal Disease on Cardiovascular Events in Patients with Chronic Kidney Disease. *Nutrients* 2022, 14, 112. https://doi.org/10.3390/nu14010012.
16. Kwan, S.Y.; Wong, H.T.; Ho, C.T.; Lee, K.H.; Wong, S.T.; Wong, C.K.; Fong, S.F.; Liu, H.; Ma, C.S.; Yiu, K.H. Impact of Periodontal Disease on Cardiovascular Events in Patients with Chronic Kidney Disease: A Systematic Review. *Nutrients* 2022, 14, 1555. https://doi.org/10.3390/nu14071555.
17. Thorman R, Neovius M, Hylander B. Clinical findings in oral health during progression of chronic kidney disease to end-stage renal disease in a Swedish population. *Scandinavian journal of urology and nephrology*, 2009; *43*(2), 154-159.
18. Akar H, Akar GC, Carrero JJ, Stenvinkel P, Lindholm B. Systemic consequences of poor oral health in chronic kidney disease patients. *Clinical Journal of the American Society of Nephrology*, 2011; *6*(1), 218-226.
19. Watanabe, K.; Tsukamoto, Y.; Takashima, M.; Yoshimura, M.; Kawai, Y. Infection and Inflammation in Chronic Kidney Disease: Impacts on Oral Health and Systemic Conditions. Nutrients 2022, 14, 4316. https://doi.org/10.3390/nu14194316.
20. Rahmati MA, Craig RG, Homel P, Kaysen GA, Levin NW: Serum markers of periodontal disease status and inflammation in hemodialysis patients. *Am J Kidney Dis* 2002; 40:983-989.

DOI : 10.62610/RJOR.2024.4.16.6

21. Manzoli, L.; Zamboni, G.; Polilli, E.; De Curtis, M.; Mariani, M.; Casciaro, P.; Tetta, C. Salivary Analysis in the Diagnosis of Systemic Diseases: A Systematic Review. *International Journal of Environmental Research and Public Health* 2021, 18, 8400. https://doi.org/10.3390/ijerph18168400.

22. Ghasemi, A.; Amiri, Z.; Amani, F.; Piri, R.; Shahabinejad, N.; Najafi, M.; Norouzi, K. Saliva: A Potential Non-Invasive Tool for the Diagnosis of Systemic Diseases. *Clinical Chemistry and Laboratory Medicine* 2022, 60, 1744-1757. https://doi.org/10.1515/cclm-2021-0463.

23. Haffajee, A.D.; Socransky, S.S.; Goodson, J.M. The Effect of Host Response Modulation on the Outcomes of Periodontal Therapy. *Journal of Periodontology* 2017, 88, 727–738. https://doi.org/10.1902/jop.2017.160698.

24. Proctor R, Kumar N, Stein A, Moles D, Porter S. Oral and dental aspects of chronic renal failure. *J Dent Res* 2005; 84:199-208.

25. Bots CP, Poorterman JH, Brand HS, Kalsbeek H, Van Amerongen BM, Veerman EC, et al. The oral health status of dentate patients with chronic renal failure undergoing dialysis therapy. *Oral Dis.* 2006 Mar;12(2):176-80.

26. Shalhoub, S.; Jablonski, M.; Azad, A.; Mavrogiannis, C.; Elsayed, M.; Thomas, R.; Heddle, N.; et al. Oral Health Status and Its Relationship with Kidney Disease in Patients Undergoing Hemodialysis. *BMC Nephrology* 2022, 23, 32. https://doi.org/10.1186/s12882-022-02781-1.

27. Ribeiro, A.B.; Lima, J.W.; Sampaio, E.M.; de Araújo, S.D.; Lima, R.R.; de Oliveira, S.M.; Leite, F.R.; da Silva, T.A.; Ribeiro, J.P. The Relationship Between Oral Health and Chronic Kidney Disease in Patients on Hemodialysis: A Cross-Sectional Study. *Clinical Oral Investigations* 2020, 24, 3093–3100. https://doi.org/10.1007/s00784-020-03338-x.

28. Esfehani, M., Keshavarzi, Z., Mirzadeh, M., Tofangchiha, M., Pagnoni, M., Patil, S., & Testarelli, L. (2023). Salivary nitric oxide levels in adults with different dmft scores in a selected iranian population: a cross-sectional study. *Acta Stomatologica Croatica*, 57(2), 113-120. https://doi.org/10.15644/asc57/2/2.

29. WHO. Oral health surveys: basic methods: World Health Organization; 2013.

30. Najafi, F., Hajizadeh, M., Soofi, M., Salimi, Y., Karyani, A., Soltani, S., … & Rezaei, S. Does socioeconomic status affect oral health? Results from the persian cohort study. *Research Square* ; 2019 https://doi.org/10.21203/rs.2.13064/v1.

31. Green J.C., Vermillion J. R. The simplified oral hygiene index. *J Am Dent Assoc*. 1964 Jan; 68:7-13.

32. Loe H, Silness J. Periodontal disease in pregnancy. I. Prevalence and severity. *Acta Odontol Scand* 1963; 21:533-551.

33. Loe H: The Gingival Index, the Plaque Index, and the Retention Index systems. *J Periodontol* 1967 (suppl 6); 38: S610-S616.

34. Page, R.C., & Eke, P.I. Case definitions for use in population-based surveillance of periodontitis. *Journal of Periodontology*, 2007; 78(7s), 1387-1399. DOI: 10.1902/jop.2007.060264.

35. Levey, A. S., Bosch, J. P., Lewis, J. B., Greene, T., Rogers, N., & Roth, D. A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. *Annals of Internal Medicine*, 1999, 130(6), 461-470. DOI: 10.7326/0003-4819-130-6-199903160-00002.

DOI : 10.62610/RJOR.2024.4.16.6

36. Kirushnan BB, Rao BS, Annigeri R, Balasubramanian S, Seshadri R, Prakash KC, Vivek V. Impact of Malnutrition, Inflammation, and Atherosclerosis on the Outcome in Hemodialysis Patients. *Indian J Nephrol*. 2017 Jul-Aug;27(4):277-283. doi: 10.4103/0971-4065.202830. PMID: 28761229; PMCID: PMC5514823.

37. Stenvinkel P, Heimburger O, Paultre F, *et al*: Strong association between malnutrition, inflammation, and atherosclerosis in chronic renal failure. *Kidney Int* 1999, 51: 1899–1911.

38. Vacariu, S. M., Adumitroaie, A. E., Șipoteanu, M. M., Anistoroaei, D., Toma, C. M., & Toma, V. Correlation between oral health status and chronic kidney disease in children. *Romanian Journal of Oral Rehabilitation*, 2023; 15(2), 450-456.

39. Stenvinkel P, Barany P, Heimburger O, Pecoits-Filho R, Lindholm B. Mortality, malnutrition and inflammation in ESRD: What is the role of interleukin-6? *Kidney Int.*, 2002, *61*(Suppl 80), S103-S108.

40. Alfano G, Perrone R, Fontana F, Ligabue G, Giovanella S, Ferrari A, Gregorini M, Cappelli G, Magistroni R, Donati G. Rethinking Chronic Kidney Disease in the Aging Population. *Life*. 2022; 12(11):1724. https://doi.org/10.3390/life12111724.

41. Stern L, Johnson RJ, Shakouri P, Athavale A, Padnick-Silver L, LaMoreaux B, Marder BA, Mandayam S. Prevalence and Influence of Gout in Patients with Advanced Chronic Kidney Disease: Findings of a Large Retrospective Chart Review. *Gout, Urate, and Crystal Deposition Disease*. 2024; 2(1):77-85. https://doi.org/10.3390/gucdd2010008.

42. Weng, R.; Yu, W.; Hong, F.; Zhang, C.; Wen, L.; Wang, F.; Luo, Y.; Ye, J.; Tang, F.; Wang, H.; et al. High Willingness to Participate in Partner Notification among Women Attending Reproductive Health and STI Clinics in Shenzhen, China: A Cross-Sectional Study. *Int. J. Environ. Res. Public Health* 2020, 17, 386. https://doi.org/10.3390/ijerph17020386.

43. Baker, M.B.; Liu, E.C.; Bully, M.A.; Hsieh, A.; Nozari, A.; Tuler, M.; Binda, D.D. Overcoming Barriers: A Comprehensive Review of Chronic Pain Management and Accessibility Challenges in Rural America. *Healthcare* 2024, 12, 1765. https://doi.org/10.3390/healthcare12171765.

44. Kadatane, S.P.; Satariano, M.; Massey, M.; Mongan, K.; Raina, R. The Role of Inflammation in CKD. *Cells* 2023, 12, 1581. https://doi.org/10.3390/cells12121581.

45. Keles, M.; Tüfekçi, S.; Arıdoğan, B.C.; Sarı, Y.; Doğan, D.; Seçilmiş, S.; Ulusoy, S.H. Salivary Changes in Patients with Chronic Kidney Disease. *Int. J. Nephrol.* 2017, 2017, 7456204. https://doi.org/10.1155/2017/7456204.

46. Sobrado Marinho JS, Tomás Carmona I, Loureiro A, Limeres Posse J, García Caballero L, Diz Dios P. Oral health status in patients with moderate-severe and terminal renal failure. *Med Oral Patol Oral Cir Bucal*. 2007 Aug 1;12(4): E305-10.

47. Bayraktar G, Kazancioglu R, Bozfakioglu S, Yildiz A, Ark E. Evaluation of salivary parameters and dental status in adult hemodialysis patients. *Clin Nephrol* 2004; 62: 380-3.

48. Kalantar Zadeh K., Block G., McAllister C.J., Humphreys M.H., Kopple J.D. Appetite and inflammation, nutrition, anemia and clinical outcome in hemodilaysis patients, *Am J Clinical Nutrition*, 2004; 80: 299-307.

49. Khan, A. A., & Haseeb, A. "Chronic Kidney Disease: A Major Risk Factor for Cardiovascular Disease." *Journal of Clinical Medicine*, 2022, 11(4), 910. https://doi.org/10.3390/jcm11040910.

50. Pérez-Gómez, M. V., et al. "Oxidative Stress in Chronic Kidney Disease: A Review." *Antioxidants*, 2023, 12(3), 541. https://doi.org/10.3390/antiox12030541.

DOI : 10.62610/RJOR.2024.4.16.6

51. Bibi G, Green Y, Nagler RM. Compositional and Oxidative Analysis in the Saliva and Serum of Predialysis Chronic Kidney Disease Patients and End-stage Renal Failure Patients on Peritoneal Dialysis. *Therapeutic Apheresis and Dialysis*, 2008; 12(2), 164-170.
52. Valko, M.; Leibfritz, D.; Moncol, J.; Cronin, M.T.; Mazúr, M.; Telser, J. Free radicals and antioxidants in normal physiological functions and human disease. *Int. J. Biochem. Cell Biol*. 2007, 39, 44–84. https://doi.org/10.1016/j.biocel.2006.07.001.
53. Buhlin K, Barany P, Heimburger O, Stenvikel P, Gustafsson A. Oral health and proinflamatory status in end-stage renal disease patients. *Oral Health Prevent Dent* 2007; 5:235-244.
54. Al-Wahadni A, Al-Omari MA. Dental diseases in a Jordanian population on renal dialysis. *Quintessence Int* 2003; 34:343-7.
55. Silva DF, Oliveira ICR, Medeiros SA, Baeder FM, Albuquerque ACL, Lima EO. Oral health challenges in patients with chronic kidney disease: A comprehensive clinical assessment. *Saudi Dent J.* 2024 Feb;36(2):364-367. doi: 10.1016/j.sdentj.2023.11.026. Epub 2023 Nov 27. PMID: 38419998; PMCID: PMC10897613.
56. Menezes CR, Pereira AL, Ribeiro CC, Chaves CO, Guerra RN, Thomaz ÉB, Monteiro-Neto V, Alves CM. Is there association between chronic kidney disease and dental caries? A case-controlled study. *Med Oral Patol Oral Cir Bucal.* 2019 Mar 1;24(2):e211-e216. doi: 10.4317/medoral.22737. PMID: 30818314; PMCID: PMC6441594.
57. https://www.who.int/team/noncommunicable-diseases/global-status-report-on-oral-health-2022.
58. Atassi F, Almas K. Oral hygiene profile of subjects on renal dialysis. *Indian J Dent Res* 2001;12: 71-76.
59. Naugle K, Darby M L, Bauman DB, Lineberger LT and Powers R. The oral health status of individuals on renal dialysis. *Ann Periodontol* 1998; 3, 197-205.
60. Gavalda C, Bagan J, Scully C, Silvestre F, Milian M, Jiminez Y. Renal hemodialysis patients: oral, salivary, dental and periodontal findings in 105 adult cases. *Oral Dis* 1999; 5: 299–302.
61. Souza, C.M., Castilho, A., and García, O. "Association Between Oral Health and Kidney Disease: The Role of Periodontal Health in Systemic Inflammation and Chronic Kidney Disease Progression." *Journal of Clinical Periodontology*, vol. 44, no. 2, 2017, pp. 178–186.
62. Atassi, F.; Al-Sharif, F.; Zakout, R.; Al-Nafea, S.; Farah, R.; Manji, F. Oral Health Status and Oral Health-Related Quality of Life in Patients with Chronic Kidney Disease. *BMC Oral Health* 2020, 20(1), 156. doi:10.1186/s12903-020-01135-6.
63. Bayraktar, G.; Kurtulus, I.; Kazancioglu, R.; Yildiz, A.; Bozfakioglu, S.; Yildiz, S.; Issever, H. Evaluation of Periodontal Parameters in Patients Undergoing Peritoneal Dialysis or Hemodialysis. *Oral Diseases* 2008, 14(2), 185–189. doi:10.1111/j.1601-0825.2007.01362.x.
64. Souza MC, Braosi APR, Luczyszyn SM, Casagrande RW, Pecoits-Filho R, Riella MC, Ignacio SA, Trevilatto PC. Oral health in Brazilians patients with chronic renal disease. *Rev Méd Chile* 2008; 136: 741-746.
65. Epstein SR, Mandel I, Scopp IW. Salivary composition and calculus formation in patients undergoing hemodialysis. *J Periodontol* 1980; 51: 336-8.
66. Chamani G, Zarei MR, Radvar M, Rashidfarrokhi F, Razazpour F. Oral health status of dialysis patients based on their renal dialysis history in Kerman, Iran. *Oral Health Prev Dent*, 2009; *7*(3): 269-75.
67. Craig RG, Kotanko P, Kamer AR, Levin NW. Periodontal diseases--a modifiable source of systemic inflammation for the end-stage renal disease patient on haemodialysis therapy? *Nephrol Dial Transplant.* 2007;22:312-5.

DOI : 10.62610/RJOR.2024.4.16.6

68. Craig RG, Spittle MA, Levin NW. Importance of periodontal disease in the kidney patient. *Blood Purif.* 2002;20:113-9.
69. Eke PI, Dye BA, Wei L, Thornton-Evans GO, Genco RJ. Prevalence of periodontitis in adults in the United States: 2009 and 2010. *Journal of dental research*, 2012; *91*(10), 914-920.
70. World Health Organization. (2022). Global oral health status report: Towards universal health coverage for oral health by 2030. World Health Organization.
71. Graziani F, Cei S, La Ferla F, Vano M, Gabriele M, Tonetti M. Effects of non-surgical periodontal therapy on the glomerular filtration rate of the kidney: an exploratory trial. *Journal of clinical periodontology*, 2010; *37*(7), 638-643.
72. Zhang, H.; Dhalla, N.S. The Role of Pro-Inflammatory Cytokines in the Pathogenesis of Cardiovascular Disease. *Int. J. Mol. Sci*. 2024, 25, 1082. https://doi.org/10.3390/ijms25021082.

DOI : 10.62610/RJOR.2024.4.16.6