

Article

Chronic Kidney Disease and Oral Health: A Cross-Sectional Study

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Abstract

Objective: This pilot study investigated the association between chronic kidney disease (CKD) and oral health, focusing on the prevalence and severity of periodontal disease (PD) in the different CKD stages. Moreover, we explored how systemic alterations related to kidney dysfunction may influence oral conditions. **Methods:** A cross-sectional observational study was conducted on seventy-five adult CKD patients (stages G1–G5) under conservative therapy. Participants underwent clinical, biochemical, and dental assessments. Periodontal parameters, such as the plaque index, bleeding on probing, clinical attachment loss, and gingival recession, were evaluated. **Results:** A significant inverse relationship was found between the estimated glomerular filtration rate (e-GFR) and PD severity, plaque index, and gingival inflammation. Advanced CKD patients exhibited a higher prevalence of generalized gingivitis and more severe PD stages and grades. Patients with e-GFR below 44 mL/min/1.73 m² had a 3.3-fold higher risk of developing PD. In our population, the prevalence of xerostomia and dysgeusia was 45% and 15%, respectively, with taste alteration correlating directly with declining kidney function. **Conclusions:** CKD patients demonstrate compromised oral health, with an increased risk of PD. Renal dysfunction appears to be a significant factor influencing the onset and progression of PD. Further studies are necessary to clarify the underlying mechanisms and to develop integrated management strategies.

Keywords: chronic kidney disease; oral health; periodontal disease



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1. Introduction

Chronic kidney disease (CKD) represents a significant problem for world public health, whose diffusion is destined to rise [1]. Currently, it affects approximately 10% of the world's

population and, according to recent epidemiological data, it will become the fifth cause of death by 2040 [2,3].

CKD is characterized by a progressive and irreversible reduction in kidney function. Its diagnosis is made in the presence of a glomerular filtration rate (GFR) reduction or of impairment biomarkers of kidney damage (such as albuminuria, hematuria, etc.), detected for at least 3 consecutive months [4]. CKD is associated with a significant increase in morbidity and mortality, above all for cardiovascular causes, and it foresees high social and economic costs, especially for the treatment of end-stage kidney disease (ESKD) patients [5]. CKD shows a multifactorial etiology; indeed, there are several risk factors that may contribute to increase its onset. In particular, the main CKD risk factors are (i) age, as the CKD prevalence seems to increase linearly with it; (ii) gender, as CKD seems to affect more women than men [6], even if the CKD progression is more rapid in male compared to female patients [7–9]; (iii) ethnicity, as the CKD incidence and prevalence seem to be higher among the African American population than among the Caucasian population; (iv) level of education, as the CKD incidence seems to be lower in the population with higher levels of education; (v) the presence of comorbidities, first of all obesity, diabetes mellitus, and arterial hypertension [10–13].

Recent epidemiological studies suggest that CKD predisposes to a higher risk for oral diseases compared to the general population. In fact, there seems to be a bidirectional relationship between oral diseases and CKD, for which the occurrence of one predisposes to the onset of the other [14]. The most common oral diseases in CKD patients are periodontal disease (PD), reduced mineralization of the bone matrix, gingival hyperplasia, and alteration of saliva secretion and composition. In addition, CKD patients show a higher susceptibility to oral infections (Table 1) [15].

Table 1. Main CKD pathways related to oral diseases.

Alterations Related to CKD	Oral Injuries	Reference
The urea and other uremic toxin accumulation in the saliva.	Xerostomia and uremic halitosis. Indoxyl sulfate enhances the survival and responses of macrophages and lymphocytes, inducing alveolar bone loss.	[16,17]
The normochromic and normocytic anemia.	Paleness of the gingival mucosa.	[18]
Calcium–phosphorus metabolism impairments.	Dental hard tissue anomalies (including hypoplasia of the dental enamel and increased susceptibility to tooth decay) or oral bone tissue alteration (including demineralization of the alveolar bone, fracture of the jaw, abnormal bone healing after an extraction, and tooth mobility due to a bone substance loss).	[19]
Uremic gastritis.	Gastroesophageal reflux, gastrointestinal lesions, and <i>Helicobacter pylori</i> infection that contribute to the onset of oral lesions and dental caries.	[20,21]
Chronic low-grade inflammation and oxidative stress.	High risk to develop periodontal disease.	[22]

Among the most common oral cavity pathologies in CKD patients, PD is frequent. In fact, the latter is a pathological condition that affects the periodontium, which is the set of structures supporting the tooth, including the gums, alveolar bone, cementum, and periodontal ligament. PD is characterized by a chronic inflammatory state that can invade

tissues at different levels. If the inflammation is localized to the gums, it is called gingivitis, which is due to the accumulation of bacteria and debris between the gum line and the tooth. If the inflammation becomes chronic and affects also the deeper tissues, invading the surrounding periodontium, it can become irreversible and is known as periodontitis [23]. It has been observed that PD presence can increase the risk of CKD onset and accelerate its progression. PD causes an alteration of the oral microbiota; in turn, the onset of oral dysbiosis induces a local increase in inflammatory molecule production (such as tumor necrosis factor-TNF- α , interleukin-IL-1 β , IL-6, and prostaglandin-PGE2) which, entering the bloodstream, are responsible for the onset of the systemic inflammatory state [24]. The latter represents an important key factor for the CKD progression. Several studies pointed out that patients with periodontitis show high levels of inflammatory mediators, which can exacerbate the systemic inflammatory state that characterizes several chronic pathologies, including CKD [25]. In addition, because periodontal pathogens can spread into the bloodstream, it is hypothesized that they can reach the kidney and can induce several mechanisms that alter the nephrons structurally and functionally [26]. Specifically, inflammatory cytokines and bacterial lipopolysaccharides (LPSs) activate nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ Bs), a transcription factor crucial to the immune response. Once activated, NF- κ B translocates to the nucleus and promotes the transcription of inflammatory genes (TNF- α , IL-6, intercellular adhesion molecule—ICAM-1, and monocyte chemoattractant protein—MCP-1). In CKD, this activation occurs primarily in renal tubular cells and glomerular mesangial cells. The persistent NF- κ B activation induces the expression of the transforming growth factor beta 1 (TGF- β 1), a potent pro-fibrotic mediator that induces interstitial fibrosis and glomerulosclerosis [27–29].

The main aim of this study is to investigate the potential correlation between CKD and oral diseases, with a particular focus on PD. Given the increasing evidence in the literature suggesting a bidirectional relationship between CKD and oral health, this study aims to assess how the severity of CKD correlates with the presence and progression of periodontal pathological conditions and other oral manifestations.

2. Materials and Methods

This cross-sectional observational study involved the enrollment of seventy-five CKD patients (40 males and 35 females) in stages G1–G5 (according to K-DIGO guidelines [4]) under conservative therapy.

Inclusion criteria were

- Diagnosis of CKD (stage G1–G5) under conservative therapy;
- Age $\geq$ 18 years;
- Both sexes;
- Acceptance and signature of informed consent.

Exclusion criteria included

- Cancer in the active phase;
- Positivity for human immunodeficiency virus (HIV), hepatitis B surface antigen (HB-sAg), or hepatitis C virus (HCV);
- Inflammatory or infectious diseases in the acute phase;
- Refusal to provide informed consent.

The clinical study was approved by the Independent Ethical Committee of Policlinico Tor Vergata (protocol no. 392-61/10 of 2022), and it was conducted in compliance with the Declaration of Helsinki and the relevant national and international regulations. All participants received detailed information regarding the study objectives and procedures, and signed a written informed consent form, ensuring the protection of their personal

data. The clinical study was carried out at the Policlinico Tor Vergata in Rome, Italy, and involved the collaboration of both the UOSD of Nephrology and Dialysis and the Special Care Dentistry Unit. We determined the sample size to ensure that the two-sided 95% confidence interval around the estimated prevalence of the primary dichotomous outcome (periodontitis, yes/no) would be sufficiently narrow for interpretation. We prespecified a maximum margin of error of ± 12 percentage points. To take a conservative approach, we assumed a prevalence of 50%, which yields the largest required sample for a given margin. Under these assumptions, standard methods for single-proportion estimation indicated a minimum of 67 participants. We overall enrolled 75 participants, which was expected to produce a 95% confidence interval with a margin of error of approximately ± 11.3 percentage points, meeting the prespecified criterion.

2.1. Clinical–Instrumental Evaluation

At the time of enrollment, detailed medical histories were collected for all patients. In particular, the laboratory parameters evaluated included complete blood count, serum creatinine, azotemia, serum electrolytes (sodium, potassium, calcium, and phosphorus), serum albumin, serum glucose, uric acid, parathyroid hormone, and lipid profile (low density lipoprotein—LDL cholesterol, high-density lipoprotein—HDL cholesterol, total cholesterol, and triglycerides). Urinalysis was also performed.

Moreover, anthropometric measurements (body weight, stature, and body mass index—BMI) and body composition evaluation via bioelectrical impedance analysis (BIA) were performed. In particular, the body weight (kg) and stature (m) of the enrolled patients were collected by using a Seca scale with a built-in stadiometer (model 700, Hamburg, Germany). BMI was calculated with the following formula: body weight (kg)/stature² (m). The measurements were recorded to the nearest 0.01 kg for body weight and 0.1 cm for stature. The BIA was performed by EGF Plus[®], software Bodygram Plus enterprise (Estor, Pero, MI, Italy), based on the bioelectrical impedance vector analysis (BIVA) technology at 50 kHz frequency. The following parameters were recorded: resistance, reactance, phase angle, total body water (TBW%), extracellular water (ECW%), intracellular water (ICW%), fat mass (FM%), fat-free mass (FFM%), body cell mass (BCM%), and basal metabolism rate (BMR).

2.2. Dental Evaluation

All patients underwent a standardized and comprehensive dental examination, which was always performed by the same examiner (M.B.) with more than ten years clinical experience in periodontology, in order to reduce possible bias.

The CP15 University of North Carolina periodontal probe, with a round tip and millimeter markings up to 15 mm, was used to record periodontal parameters on a standardized periodontal chart. The following clinical indices were assessed: decayed, missing, filled teeth (DMFT); plaque index (PI), determined after application of plaque-disclosing tablets and recorded on all teeth; bleeding on probing (BoP), evaluated dichotomously within 30 s after gentle probing at six sites per tooth; periodontal pocket depth (PPD) and gingival recession (REC), both measured to the nearest millimeter at six sites per tooth; and clinical attachment loss (CAL), calculated as the sum of PPD and REC. In addition, each participant completed a questionnaire investigating the frequency and methods of domiciliary oral hygiene, the regularity of dental check-ups, self-reported oral symptoms (such as halitosis, tooth mobility, xerostomia, and dysgeusia), and lifestyle habits, including smoking and alcohol consumption (Supplementary Materials) [30].

2.3. Statistical Analysis

All statistical analyses were performed by an independent investigator (G.T.) using Stata 16.0 software (StataCorp LLC, College Station, TX, USA) and GraphPad Prism 10 (GraphPad Software, San Diego, CA, USA). Descriptive statistics were reported as frequencies (and percentages) for categorical variables and as means $\pm$ standard deviations for continuous variables. The Shapiro–Wilk test was used to evaluate the normality of continuous data. Univariate logistic regression models were then employed to assess the association between each clinical index and periodontitis severity, which was determined by stage and grade, and subsequently dichotomized. Statistical significance was set at $p < 0.05$.

3. Results

The mean age of the study population was 66.9 ± 14.4 years. The study population was initially divided into two subgroups based on the value of the estimated glomerular filtration rate (e-GFR). In particular, an e-GFR value of $60 \text{ mL/min/1.73 m}^2$ was used as the cut-off, since the CKD diagnosis, in the absence of other markers of renal damage, is made for values $\leq 60 \text{ mL/min/1.73 m}^2$ detected for at least 3 consecutive months [4]. Subsequently, since the later stages had a larger number of enrolled patients, we decided to treat them separately. In Table 2, we report the features of the study population, divided according to the CKD stage.

Table 2. Features of study population, divided according to chronic kidney disease (CKD) stage.

CKD STAGE	tot. (n)	%	Gender (Male/Female)	Mean Age (Years) *
G1-2	14	18.7	(10/4)	54.14 ± 11.51
G3a	10	13.3	(6/4)	70.50 ± 8.54
G3b	23	30.7	(11/12)	72.04 ± 11.72
G4	19	25.3	(7/12)	72.84 ± 11.11
G5	9	12.0	(6/3)	57.00 ± 19.78

* Values are expressed as mean $\pm$ standard deviation.

Tables 3 and 4 show the biochemical parameters and the body composition of the patients enrolled in the trial, respectively.

Table 3. Biochemical parameters of enrolled patients, divided by CKD stage.

Parameter	Stage G1–2	Stage G3a	Stage G3b	Stage G4	Stage G5
Red blood cells (millions/ μL)	5.01 ± 0.46	4.77 ± 0.76	4.18 ± 0.64	3.97 ± 0.44	3.88 ± 0.97
Hemoglobin (g/dL)	14.99 ± 0.98	13.93 ± 1.95	12.38 ± 2.58	11.48 ± 1.39	11.32 ± 2.02
White blood cells (thousands/ μL)	6.39 ± 1.98	6.26 ± 1.90	7.86 ± 5.70	7.45 ± 2.33	5.55 ± 1.00
Platelets (thousands/ μL)	233.29 ± 96.18	248.00 ± 71.57	234.61 ± 69.31	228.84 ± 69.35	193.11 ± 43.37
Creatinine (mg/dL)	10.04 ± 0.20	1.19 ± 0.12	1.68 ± 0.30	2.19 ± 0.66	6.72 ± 4.15

Table 3. *Cont.*

Parameter	Stage G1–2	Stage G3a	Stage G3b	Stage G4	Stage G5
e-GFR (mL/min/1.73 m ²)	76.46 ± 13.82	54.89 ± 3.62	36.10 ± 5.40	23.54 ± 3.56	10.34 ± 4.40
Azotemia (mg/dL)	42.31 ± 9.65	47.00 ± 12.56	72.62 ± 23.67	90.52 ± 38.71	130.22 ± 41.20
Glycaemia (mg/dL)	91.79 ± 19.01	88.60 ± 12.25	104.62 ± 22.04	95.20 ± 24.41	98.38 ± 27.14
Uric acid (mg/dL)	6.07 ± 1.53	4.43 ± 1.11	5.28 ± 2.22	5.03 ± 1.91	6.38 ± 1.15
Albumin (mg/dL)	4.39 ± 0.42	4.53 ± 0.65	4.53 ± 0.56	4.20 ± 0.26	4.29 ± 0.49
Sodium (mmol/L)	140.69 ± 1.84	141.67 ± 2.06	140.57 ± 2.84	139.20 ± 4.95	141.22 ± 3.30
Potassium (mmol/L)	4.55 ± 0.42	4.64 ± 0.48	4.64 ± 0.52	4.69 ± 0.66	5.36 ± 0.78
Calcium (mmol/L)	9.54 ± 0.51	8.86 ± 2.05	9.47 ± 0.59	9.10 ± 1.20	8.89 ± 0.85
Phosphorus (mmol/L)	3.12 ± 0.40	3.24 ± 0.53	3.36 ± 0.84	3.66 ± 0.57	4.90 ± 1.27
Total cholesterol (mg/dL)	191.00 ± 41.78	186.50 ± 44.93	172.74 ± 51.03	167.00 ± 26.87	151.2 ± 37.35
HDL-cholesterol (mg/dL)	49.55 ± 14.31	50.87 ± 12.76	47.79 ± 15.22	54.30 ± 26.26	43.80 ± 7.79
LDL-cholesterol (mg/dL)	117.88 ± 38.54	109.00 ± 34.67	96.79 ± 37.87	93.10 ± 36.03	89.12 ± 29.35
Triglycerides (mg/dL)	112.92 ± 46.81	108.20 ± 40.41	135.06 ± 93.36	114.27 ± 46.22	122.4 ± 62.63
Parathyroid hormone (pmol/L)	89.75 ± 68.29	105.87 ± 33.25	86.57 ± 57.01	151.75 ± 89.99	604.27 ± 954.74

Values are expressed as mean ± standard deviation. Abbreviations: e-GFR, estimated glomerular filtration rate; HDL-cholesterol, high-density lipoprotein; LDL-cholesterol, low-density lipoprotein.

Table 4. Body composition parameters of enrolled patients, divided according to CKD stage.

Parameter	Stage G1–2	Stage G3a	Stage G3b	Stage G4	Stage G5
BMI (kg/m ²)	26.88 ± 5.39	27.28 ± 4.98	28.89 ± 6.18	27.42 ± 6.31	25.46 ± 3.54
Resistance (Ω)	498.86 ± 69.84	500.10 ± 74.43	485.77 ± 100.24	509.24 ± 95.73	487.50 ± 75.95
Reactance (Ω)	52.14 ± 16.24	40.20 ± 11.19	43.94 ± 11.10	42.49 ± 13.29	39.19 ± 12.33
Phase Angle (°)	5.98 ± 1.85	4.69 ± 1.35	5.13 ± 1.41	4.73 ± 1.03	4.53 ± 1.09
TBW %	54.28 ± 7.83	54.12 ± 6.22	53.17 ± 6.26	52.81 ± 6.43	55.84 ± 9.33
ICW %	52.59 ± 7.74	46.07 ± 9.39	49.08 ± 7.24	48.32 ± 4.76	44.95 ± 8.07
ECW %	47.00 ± 7.61	51.91 ± 12.04	51.09 ± 7.32	53.14 ± 6.53	51.24 ± 14.26
FM %	26.22 ± 9.85	29.02 ± 9.48	28.21 ± 7.54	30.51 ± 9.04	24.23 ± 10.42

Table 4. Cont.

Parameter	Stage G1–2	Stage G3a	Stage G3b	Stage G4	Stage G5
FFM %	73.78 ± 9.85	70.98 ± 9.48	71.79 ± 7.54	69.49 ± 9.04	66.48 ± 23.61
BCM %	52.54 ± 8.44	44.97 ± 10.05	48.06 ± 7.88	45.86 ± 6.92	44.53 ± 7.32
BMR (Kcal/day)	1620.56 ± 258.0	1426.30 ± 214.58	1506.41 ± 254.03	1391.48 ± 151.93	1445.18 ± 138.48
ASMM (kg)	26.3 ± 3.9	25.7 ± 3.3	26.3 ± 5.2	24.7 ± 3.6	26.5 ± 4.1
ASMI (kg/m ²)	9.1 ± 0.9	9.8 ± 1.0	10.2 ± 1.2	10.0 ± 1.5	9.3 ± 1.6

Values are expressed as mean ± standard deviation. Abbreviations: ASMI, appendicular skeletal muscle mass index; ASMM, appendicular skeletal muscle mass; BCM, body cell mass; BMI, body mass index; BMR, basal metabolism rate; ECW, extracellular water; FFM, fat free mass; FM, fat mass; ICW, intracellular water; TBW, total body water.

In Table 5, we present the total number of enrolled patients for each CKD stage, the number of edentulous patients, the percentage of sites with a periodontal pocket depth > 3 mm, and the percentage of sites with gingival recessions > 1 mm.

Table 5. Number of edentulous patients, percentage of sites with periodontal pocket depth > 3 mm, and percentage of sites with gingival recessions > 1 mm according to CKD stage.

CKD Stage	Total Number of Patients	Number of Edentulous Patients	% of Sites with Periodontal Pocket Depth > 3 mm	% of Sites With Gingival Recessions > 1 mm
G1–2	14	1	10.86	19.53
G3a	10	1	31.88	32.44
G3b	23	3	19.75	32.20
G4	19	4	23.81	38.37
G5	9	1	19.63	45.88

In Table 6, we present the percentage of localized gingivitis and the percentage of generalized gingivitis, identified by full-mouth bleeding score (FMBS) values. Moreover, we report the percentage of PI, identified by full-mouth plaque score (FMPS) values, for each CKD stage of the enrolled patients.

Table 6. Distribution of localized and generalized gingivitis and of plaque index according to CKD stage.

CKD Stage	% Localized Gingivitis (10% < FMBS < 30%)	% Generalized Gingivitis (FMBS > 30%)	% Plaque Index
G1–2	14	64	45
G3a	50	40	86
G3b	20	67	75
G4	26	52	85
G5	20	80	77

Abbreviations: FMBS, full-mouth bleeding score.

According to the new classification of periodontal and peri-implant diseases and conditions [31], we divided the CKD population based on the PD stage as follows: 31.3%

in stage I, 19.4% in stage II, 19.4% in stage III, 28.3% in stage IV, and 1.6% without PD. Moreover, the same population was divided according to the PD grade: 53.7% grade I, 35.8% in grade II and 8.9% in grade III, and 1.6% without PD (Table 7).

Table 7. Enrolled CKD population divided according to the periodontal disease stage and grade.

PD Classification		Percentage (%)
PD Stage	Stage I	31.3
	Stage II	19.4
	Stage III	19.4
	Stage IV	28.3
	No PD	1.6
PD Grade	Grade I	53.7
	Grade II	35.8
	Grade III	8.9
	No PD	1.6

We observed a significant direct correlation between age and PD ($p = 0.016$). Moreover, we pointed out an indirect association between the presence of PD and e-GFR ($p = 0.038$), and, in particular, with the grade of PD ($p = 0.029$). Moreover, patients with a lower e-GFR (<44 mL/min, stage G3b of CKD) showed a 3.3-fold increased risk of developing PD (Figure 1).

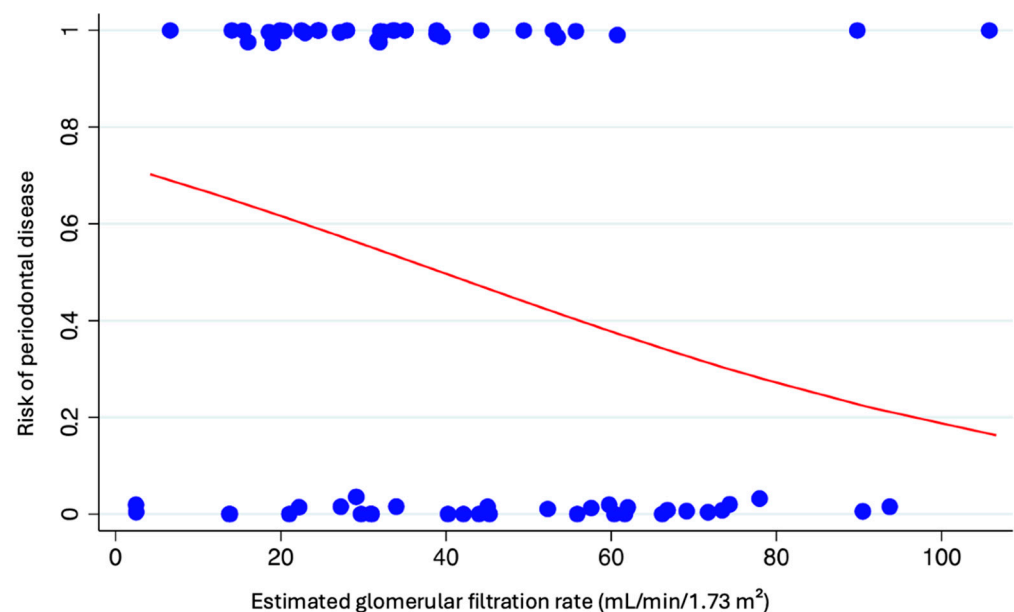


Figure 1. Risk of periodontal disease (PD) onset based on estimated glomerular filtration rate (eGFR).

We also performed a multivariate regression model. Model 1 treats the renal function as a continuous variable: every 10 mL/min/1.73 m² decrease in eGFR increases the likelihood of severe periodontitis by 39%, regardless of age, sex, diabetes mellitus, and smoking.

Model 2 instead uses a clinical threshold (eGFR < 44 mL/min/1.73 m² $\approx$ CKD stage G3b or worse). In this case, the moderate-to-advanced CKD is associated with a 3.7-fold increased risk of severe periodontitis (Table 8; Figure 2).

Table 8. Results of the multivariate analysis.

Predictor	Model 1: Severe PD ~ eGFR per 10↓ (N = 67)	Model 2: Severe PD ~ eGFR < 44 (N = 67)
CKD variable	OR 1.39 (95% CI 1.04–1.86), $p = 0.027^*$	OR 3.74 (95% CI 1.10–12.77), $p = 0.035^*$
Age (per year)	OR 1.04 (0.998–1.09), $p = 0.060$	OR 1.05 (1.001–1.095), $p = 0.045^*$
Male sex	OR 0.59 (0.18–1.88), $p = 0.370$	OR 0.71 (0.23–2.23), $p = 0.556$
Current smoker	OR 2.57 (0.74–8.90), $p = 0.136$	OR 2.55 (0.75–8.69), $p = 0.134$
Diabetes	OR 5.13 (1.22–21.6), $p = 0.026^*$	OR 4.13 (1.08–15.8), $p = 0.038^*$

* p -value < 0.05 is considered statistically significant.

Forest plot of multivariate logistic regression models

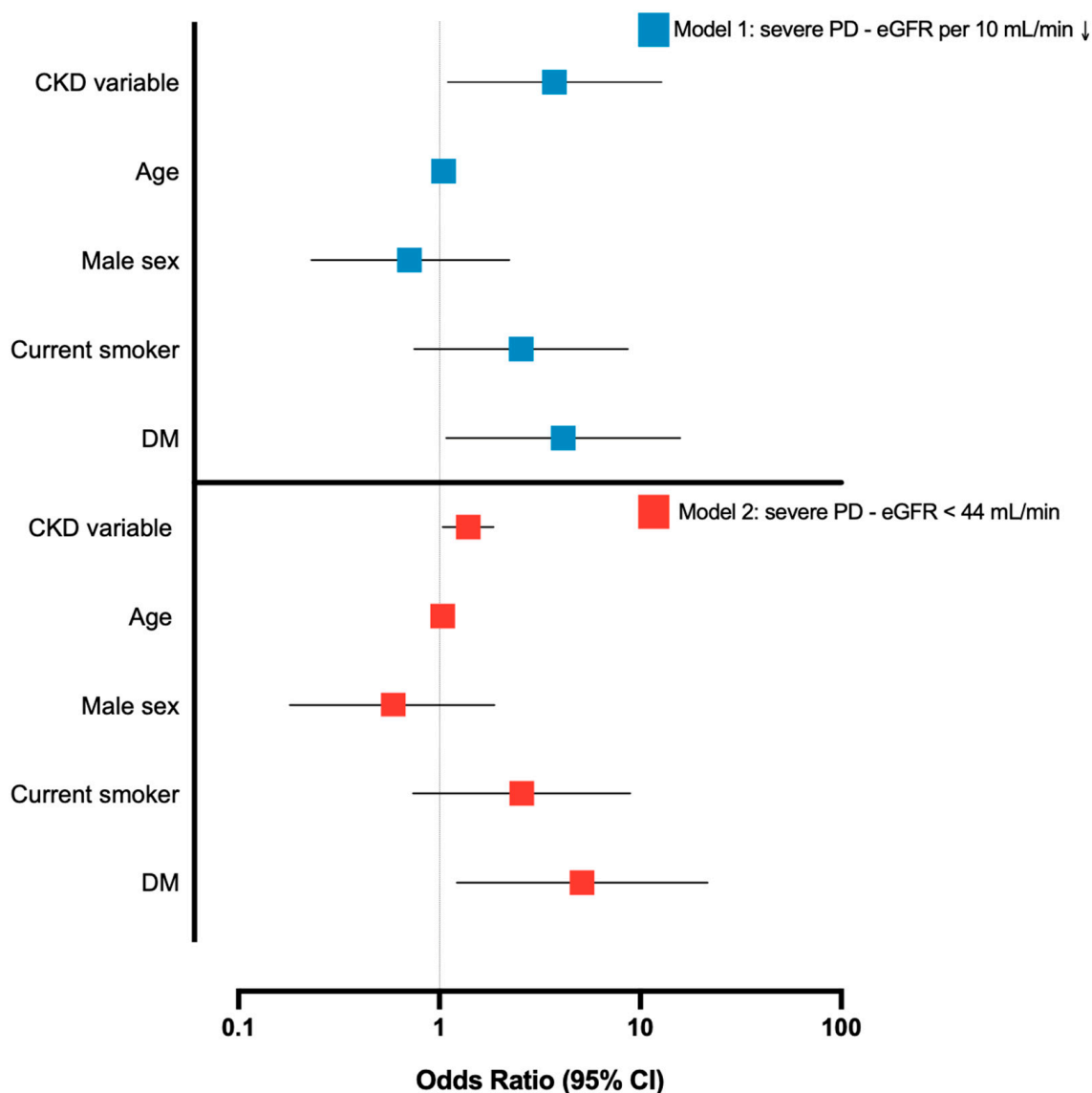


Figure 2. Forest plot of multivariate logistic regression models. Abbreviations: CI, confidence interval; CKD, chronic kidney disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; PD, periodontal disease; ↓, decrease.

We calculated the prevalence of other oral diseases, with xerostomia at 45% and dysgeusia at 15%. A direct correlation was highlighted between e-GFR values and the presence of dysgeusia ($R = 0.34$).

Finally, we performed a correlation analysis between body composition parameters and periodontal parameters (Figure 3). Particularly, in CKD patients with stage G1 and G2, we detected an indirect correlation between skeletal muscle mass (ASMM) and PD stage ($R^2 = 0.4$; $p = 0.0187$), while, in CKD stage G3b, we observed an indirect correlation between ASMM and FMBS ($R^2 = 0.2$; $p = 0.0385$), and between appendicular skeletal muscle mass index (ASMI) and FMPS ($R^2 = 0.2$; $p = 0.0461$).

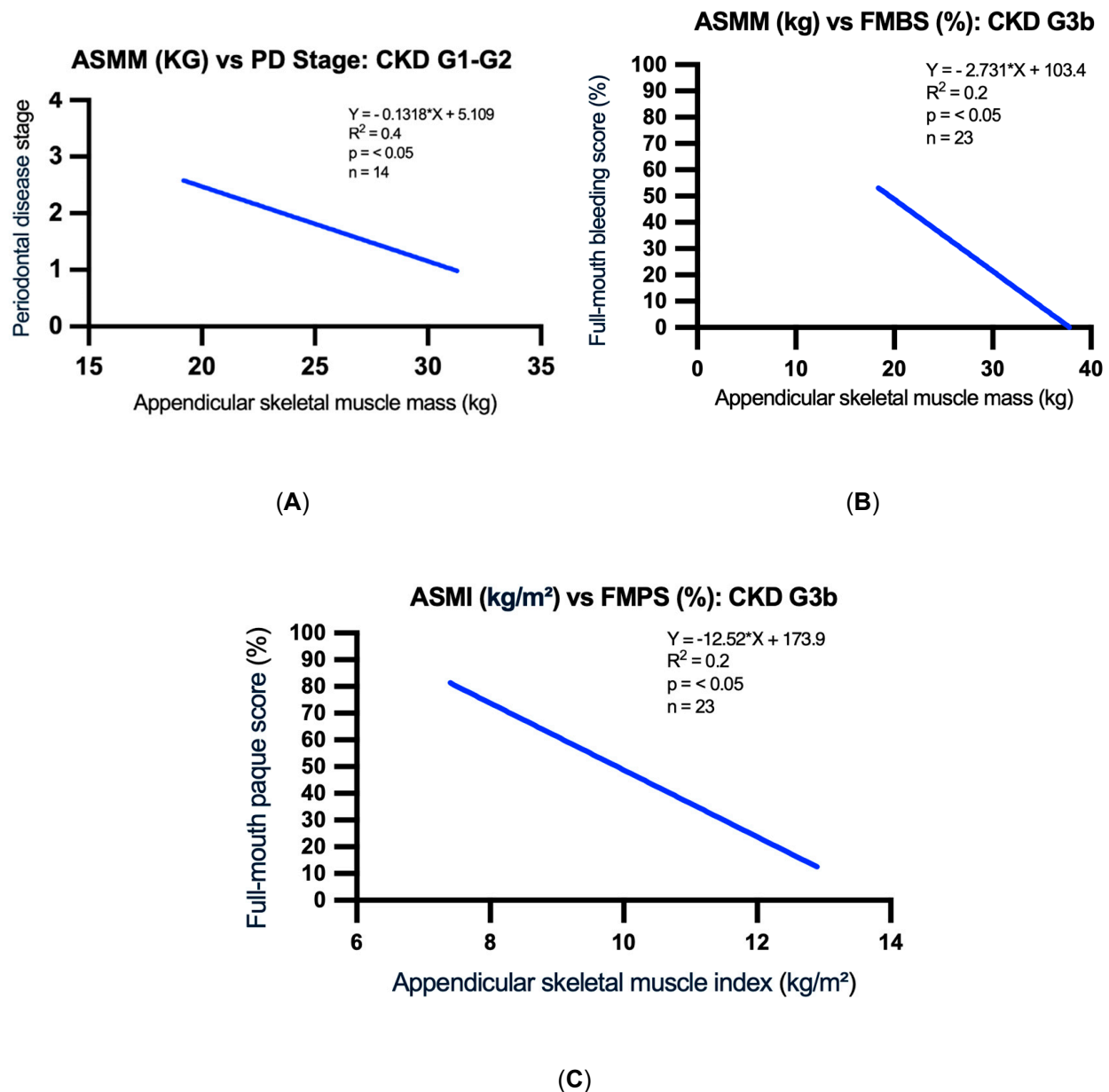


Figure 3. Simple linear regression between appendicular skeletal muscle mass (kg) and periodontal disease stage in stages G1–G2 of CKD (A); appendicular skeletal muscle mass (kg) and full-mouth bleeding score (%) in stage G3b of CKD (B); appendicular skeletal muscle index and full-mouth plaque score in stage G3b of CKD (C).

4. Discussion

Our cross-sectional study aimed to confirm the correlation between CKD and oral diseases; in fact, from numerous studies in the literature, there seems to be a bidirectional correlation between the two pathologies, in which the presence of one predisposes to the onset of the other [14,32–34].

This correlation has been found in in vitro studies as well as in clinical ones. It is very important to underline that the saliva and oral microbiota composition is influenced by the presence of chronic degenerative non-communicable diseases, such as CKD [35]. Specifically, in a CKD animal model, Randall et al. demonstrated that kidney disease alters the biochemical composition of saliva and induces a progressive dysbiosis of the oral microbiota. In fact, they showed that the transfer of oral microbiota from CKD rats in germ-free animals with normal renal function induces PD [35].

Recent epidemiological studies highlighted that CKD patients have a significantly higher prevalence of oral diseases and their progression rate was indirectly correlated to eGFR. The main causes of this predisposition include the following: (i) The accumulation of urea and other uremic toxins in the saliva, which are responsible for xerostomia, oral microbiota alterations, uremic halitosis, and dry mouth [16]. Uremic toxins are capable of modifying the immune system's response to infections. In fact, indoxyl sulfate enhanced the survival and responses of macrophages and lymphocytes to *Porphyromonas gingivalis*, inducing alveolar bone loss [17]. (ii) Normochromic and normocytic anemia, responsible for the paleness of the gingival mucosa [18]. (iii) Alterations in calcium–phosphorus metabolism, responsible for dental tissues anomalies (including hypoplasia of the dental enamel, and increased susceptibility to tooth decay) or oral bone tissue alteration (including demineralization of the alveolar bone, fracture of the jaw, abnormal bone healing after an extraction, and tooth mobility due to the bone substance loss) [19]. (iv) Uremic gastritis, which induces gastroesophageal reflux, gastrointestinal lesions, and *Helicobacter pylori* infection, which contribute to the onset of oral lesions and dental caries [20,21]. (v) Chronic low-grade inflammation and oxidative stress, which predispose the oral cavity to the development to diseases with an inflammatory etiology.

In our study, we highlighted an inverse correlation between PD presence and its grade and eGFR. This result seems to be attributable to the greater susceptibility to oral cavity infections in CKD patients [15]. In this context, the main causes of PD are, as above described, the accumulation of urea and uremic toxins in saliva [16], alterations in calcium–phosphorus metabolism [19,21], the onset of uremic stomatitis and gastritis [21], and, in particular, the presence of low-grade chronic inflammation (or micro-inflammation) and oxidative stress [22]. In fact, numerous studies point out how low-grade chronic inflammation and oxidative stress, characteristic of CKD [36], can constitute the trigger factors in the onset of PD.

In our study, it also emerged that PI, identified by FMPS, had a negative correlation with eGFR. In particular, in CKD patients with G1 and G2 stages, PI was around 45%, while, starting from stage G3a, this value increased significantly, reaching 75–86%. These data support the hypothesis according to which oral health worsens with the CKD progression [25].

In a recent study, significant correlations were found between serum biomarkers of kidney function and periodontal clinical parameters [37]. Dembowska et al. showed that hemodialysis (HD) patients had a higher incidence and severity of gingivitis and periodontitis compared to the control group. They found a depth of more than 6 mm in 25% of the HD patients and in 5% of the control group. $\text{Cal} \geq 5$ mm was found in 55% of HD patients and 24% of the control group. Severe periodontitis was detected in 21% and moderate in 55% of HD patients [38]. Yang et al. demonstrated a direct correlation between

PD and CKD, underlining that the risk of periodontal tissue destruction and tooth loss in CKD patients increased over time. Based on the above-mentioned results, they suggested to consider renal function when treating the PD in patients with chronic periodontitis, as well as the need to pay attention to oral hygiene in CKD patients [39].

Furthermore, a direct correlation has been observed between patients' age and PD. With aging, the immune system undergoes a progressive and physiological deterioration, reducing its ability to adequately respond to infections, including oral ones. This puts elderly patients at higher risk of infection by the bacteria that cause PD onset. Aging brings with it a decrease in manual dexterity, which can cause difficulties in the accurate removal of plaque and tartar, caused not only by a poor attention to oral hygiene but also to the loss of motor skills, which hinder adequate dental cleaning [40].

At the same time, advancing age is often associated with significant hormonal changes that can negatively affect oral health. In addition, metabolic conditions that accompany aging, such as diabetes mellitus and metabolic syndrome, increase chronic inflammation and the risk of infections, thus further aggravating possible PD development. Another relevant physiological change observed in the geriatric population is the reduction in salivary production, which induces dry mouth, or xerostomia. Saliva plays a crucial role in protecting against oral infections by neutralizing acids, containing lysozyme, facilitating the removal of food debris, and maintaining the balance of the oral microbiota. This decrease makes the oral cavity more favorable to the proliferation of pathogenic bacteria [41]. In our study, we found a prevalence of xerostomia of 45%. The latter, often resulting from reduced salivary flow or as a side effect of polypharmacotherapy, favors the onset of mucosal lesions, opportunistic fungal infections, and makes it difficult to chew and swallow. Uremic stomatitis, although less frequent, is a specific manifestation of advanced CKD, characterized by painful ulcerative or pseudomembranous lesions.

Older adults are often subject to increased drug intake, many of which may have side effects that negatively affect oral health. Some drugs, in fact, can further reduce saliva production or alter the oral microbiota, favoring the onset of PD [42].

In our study population, we found a prevalence of dysgeusia equal to 15%, highlighting a direct correlation between eGFR values and the presence of such sensory alterations. Dysgeusia is a symptom that negatively affects the quality of life of CKD patients, especially in advanced stages. Frequently, patients describe this condition as a perception of an unpleasant or metallic taste. Numerous scientific evidence attributes the alteration of taste perception and uremic halitosis to the accumulation of uremic toxins and xerostomia, phenomena commonly observed in the context of CKD. This sensitivity impairment can lead to a reduced appetite, malnutrition onset, and weight loss, conditions that are already frequent in CKD patients and which may worsen their overall prognosis. Moreover, dysgeusia may negatively influence the adherence to dietary prescriptions, which are fundamental in CKD management [16,43].

Regarding the correlation between the periodontal parameters and body composition, for the first time in the literature, we demonstrated that ASMM and ASMI seems to be correlated with PD severity in CKD patients. In fact, in the early stages of CKD (G1-G2), we pointed out an indirect correlation between ASMM and PD stage.

In fact, a feature of CKD is uremic sarcopenia (US). Although US is more commonly associated with advanced CKD stages, evidence suggests that US is part of the clinical picture of patients with partially preserved renal function. This phenomenon can be attributed to several factors, including metabolic acidosis, insulin resistance, and chronic low-grade inflammation, which leads to the activation of the ATP-dependent ubiquitin-proteasome system, the principal proteolytic machine responsible for regulated protein degradation in eukaryotic cells [44]. This clinical implication emphasizes the importance of

periodic periodontal screening with regular follow-ups in CKD patients, since sarcopenia is associated with advanced stages of PD, suggesting a complex, bidirectional relationship in this population.

The indirect correlation between ASMM and FMBS, as well as ASMI and FMPS, observed in CKD patients of stage G3b contributes to negatively affecting periodontal health, since the mechanisms underlying the US impair both muscle mass and oral tissue health, leading to the observed correlations.

The novelty of our study is that, in CKD patients, we identified the correlation between ageusia and xerostomia at the same observation time. This simultaneous evaluation highlights a previously unexplored interaction that may provide valuable insights into the patients' disease progression. Such findings hold potential relevance for the early identification of the highest-risk patients of oral diseases progression. These oral cavity alterations may be CKD-related clinical manifestations. Therefore, if renal function has not been previously assessed in a subject with these oral cavity alterations, it would be appropriate to evaluate it. Another innovative aspect of our pilot study is the correlation between the periodontal parameters and body composition. For the first time, we demonstrated that alterations in body composition are associated with PD severity. In particular, pathological ASMM and ASMI are related with a more severe stage of PD in the early stages of CKD (G1 and G2), while, in G3b CKD patients, we observed a negative correlation between ASMM and FMBS. In fact, PD itself represents a trigger of systemic inflammation, and it may contribute to the deterioration of muscle mass in nephropathic patients. This novel finding underscores the bidirectional interplay between oral and systemic health, suggesting that monitoring the body composition could provide additional clinical insights and help to identify patients at higher risk of adverse outcomes related to both PD and muscle wasting.

One of the main limitations of the study is the small sample size, which may limit the generalization of the findings. Future studies should include a larger sample to confirm the results and improve their clinical applicability. Moreover, it will be necessary to extend the analysis to kidney transplant recipient and dialysis patients, who are currently excluded but with a significant clinical interest, in order to understand the correlations observed in this study.

5. Conclusions

CKD patients show a significantly impaired oral health. This cross-sectional study demonstrated that renal dysfunction is an important risk factor for PD onset. In the future, it will be relevant to confirm these data and to find out the typical CKD metabolic alterations which can trigger PD.

These preliminary data highlight the importance of more frequent dental follow-ups in CKD patients, as this pathological condition appears to be a predisposing factor, similarly to other non-communicable chronic degenerative diseases, for PD. Early diagnosis of PD, therefore, allows for the prompt treatment of oral manifestations by delaying the progression and counteracting its worsening. At the same time, particularly in CKD patients who show an immunological etiopathogenesis, the presence of PD may represent a factor contributing to a more rapid progression of CKD toward ESKD.

Furthermore, our findings confirm the close correlation between systemic diseases, such as CKD, and oral pathologies. For this reason, it would be advisable to include, in addition to routine blood tests, a regular evaluation of oral health in the clinical monitoring of CKD patients, ideally at least every six months. Such an integrated screening approach is crucial, since the improvement of oral health may have positive effects not only on primary

prevention but also on the reduction in systemic complications, ultimately contributing to a better overall prognosis in CKD patients.

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