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CASE REPORT

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Status of periodontal health in German patients suffering from chronic kidney disease—Data from the GCKD study

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Abstract

Aim: To assess the prevalence and severity of periodontitis in patients with moderate chronic kidney disease (CKD) and comparing the results with the self-reported periodontitis awareness of the study subjects.

Material and methods: The periodontal status of 270 patients with moderate CKD randomly selected from a cohort of 5,217 subjects participating in the prospective observational German Chronic Kidney Disease (GCKD) project was analysed by recording bleeding on probing (BOP), probing pocket depth (PPD) and clinical attachment level (CAL). Furthermore, the awareness of the study subjects of their periodontal conditions was evaluated by a self-reported questionnaire.

Results: 24.4% of the CKD study patients showed no or only mild signs of periodontal disease, 47.6% displayed moderate and 27% severe periodontitis. Questionnaire data revealed that 62.3% of the study subjects with severe periodontitis were not aware of the presence of the disease, 44.4% denied having received any systematic periodontal therapy so far, although 50% of them indicated to visit their dentist regularly for professional tooth cleanings.

Conclusion: While the clinical study data confirm an increased prevalence of periodontitis in CKD patients, their self-reported awareness of periodontitis was low.

Dannewitz, Sommerer, Krane and Jockel-Schneider contributed equally to this manuscript.

KEYWORDS
chronic kidney disease, observational cohort study, periodontitis, risk factors

1 | INTRODUCTION

Chronic kidney disease (CKD) is recognized as a global health problem, with an estimated prevalence of 8%–16% worldwide (Jha et al., 2013). According to the 2013 Global Burden of Disease study, CKD was among the five leading causes of reduced life expectancy (GBD, 2013). Periodontal diseases, including gingivitis and periodontitis, are the most common inflammatory conditions in humans (Tonetti, Jepsen, Jin, & Otomo-Corgel, 2017). Periodontitis is a chronic inflammatory disease, closely related to a dysbiotic, inflammation-promoting change in the composition of the oral microbiota and might significantly interfere with the status of general health. An association between periodontitis and CKD has been identified by systematic review and meta-analysis. Patients with CKD or patients on maintenance dialysis treatment display an increased prevalence of bacterial plaque, calculus and gingival inflammation when compared to controls with unimpaired kidney function (Deschamps-Lenhardt, Martin-Cabezas, Hannedouche, & Huck, 2019; Kapellas, Singh, Bertotti, Nascimento, & Jamieson, 2019; Zhao et al., 2018).

The primary cause of mortality in patients with CKD is cardiovascular disease (CVD), yet effective medical strategies to reduce CV risk and to improve outcomes are lacking. CVD mortality in patients with CKD is related to an increased systemic inflammatory burden (Gansevoort et al., 2013; Go, Chertow, Fan, McCulloch, & Hsu, 2004). Periodontitis may act as a comorbid inflammatory disease in patients with CKD promoting the development of CVD (Kshirsagar et al., 2009).

Several studies have identified periodontal disease as a novel, non-traditional risk factor for CKD progression (Chambrone et al., 2013; Fisher, Taylor, Papapanou, Rahman, & Debanne, 2008; Grubbs et al., 2015; Iwasaki et al., 2012; Kapellas et al., 2019; Ruospo et al., 2014; Sharma et al., 2014; Shultis et al., 2007). However, the majority were cross-sectional and assessed the prevalence of periodontitis in individuals with end-stage renal disease (Borgnakke, 2013; Chambrone et al., 2013; Ruospo et al., 2014). So far, there was only scant information on the status of periodontal health in patients with CKD of moderate severity.

Therefore, this investigation aimed to assess the prevalence of periodontitis in patients with moderate CKD by clinical examination. Furthermore, oral symptoms related to CKD and periodontitis, periodontal disease awareness and the utilization of dental service were evaluated by self-report.

Clinical relevance

Scientific rationale for the study: Systemic inflammation associated with chronic kidney disease (CKD) may favour the development of periodontal disease.

Principal findings: In the assessed cohort of CKD patients, not requiring renal replacement therapy, periodontitis of varying severity was a very prevalent but mostly undiagnosed comorbidity despite the self-reported frequent utilization of dental services. Self-awareness of the presence of periodontitis accordingly was low.

Practical implications: CKD and severe periodontitis are both chronic inflammatory diseases, significantly contributing to the total systemic inflammatory burden. Routine assessment of periodontal health in CKD patients and assessment of renal function in severe periodontitis patients who are not amenable to standard periodontal therapy may be advisable.

2 | MATERIALS AND METHODS

2.1 | Study design and population of the GCKD study

The German Chronic Kidney Disease (GCKD) study is an ongoing prospective, cohort study in CKD patients who do not require renal replacement therapy. Details on the enrolment process and study procedure have been described elsewhere (Eckardt et al., 2012; Titze et al., 2015). Briefly, 5,217 male and female patients aged 18–74 years with moderately reduced estimated glomerular filtration rate (eGFR) of 30–60 ml/min/1.73 m^2 (corresponding to CKD stage 3) or an eGFR > 60 ml/min/1.73 m^2 and "overt" albuminuria/proteinuria at screening time were included between 2010 and 2012. Exclusion criteria comprised non-Caucasian ethnicity, active malignancy, previous transplantation, New York Heart Association Stage IV heart failure and legal restrictions. All participants provided written informed consent, and the appropriate ethics committees approved the GCKD study and the GCKD-Oral (GCKD-O) substudy. The study was registered in the national registry for clinical studies (DRKS 00003971).

2.2 | Data collection and laboratory measurements

At GCKD baseline visit, patient's medical history, socio-demographic and lifestyle factors, as well as medication intake, were obtained by personal interview using standardized questionnaires.

Blood and spot-urine samples were collected and processed as reported previously (Beck et al., 2015; Eckardt et al., 2012; Titze et al., 2015). Kidney function and impairment were assessed by eGFR and urine albumin-to-creatinine ratio (ACR), and eGFR was determined using the 4-variable MDRD formula and assigned to one of the four categories according to the KDIGO clinical practice guideline: ≥60 ml/min/1.73 m^2 (stage G1/G2), 45–59 ml/min/1.73 m^2 (stage G3a), 30–44 ml/min/1.73 m^2 (stage G3b) and 15–29 ml/min/1.73 m^2 (stage G4) ml/min/1.73 m^2 (Levey et al., 2011). Since ACR is associated with increased risk of adverse outcome and

disease progression, albuminuria was further classified according to the NICE guidance for early identification and management of CKD in adults (Carville, Wonderling, Stevens, & Guideline Development Group, 2014) into three levels: >30 mg/g (A1), 30–300 mg/g (A2) and > 300 mg/g (A3). All renal values analysed in this study were taken from the GCKD baseline visit.

2.3 | Assessment of the oral/periodontal status

Since 2012, the oral status of GCKD-study patients from Heidelberg and Würzburg was evaluated by clinical examination and a self-report questionnaire (GCKD-O).The postal survey comprised 21 items regarding oral health, periodontal status, oral hygiene attitude and behaviours, dental care utilization and the awareness of possible oral signs of CKD, including mouth dryness, mouth soreness, problems with chewing or swallowing, tongue changes and malodour. The periodontal health status of randomly selected GCKD-O patients was clinically assessed between 2012 and 2014.

Probing pocket depth (PPD) and clinical attachment level (CAL) were recorded to the nearest millimetre on all teeth excluding the third molars, by three trained and calibrated dental examiners (PS, YJ and AG). The presence of bleeding (BOP) was assessed dichotomously.

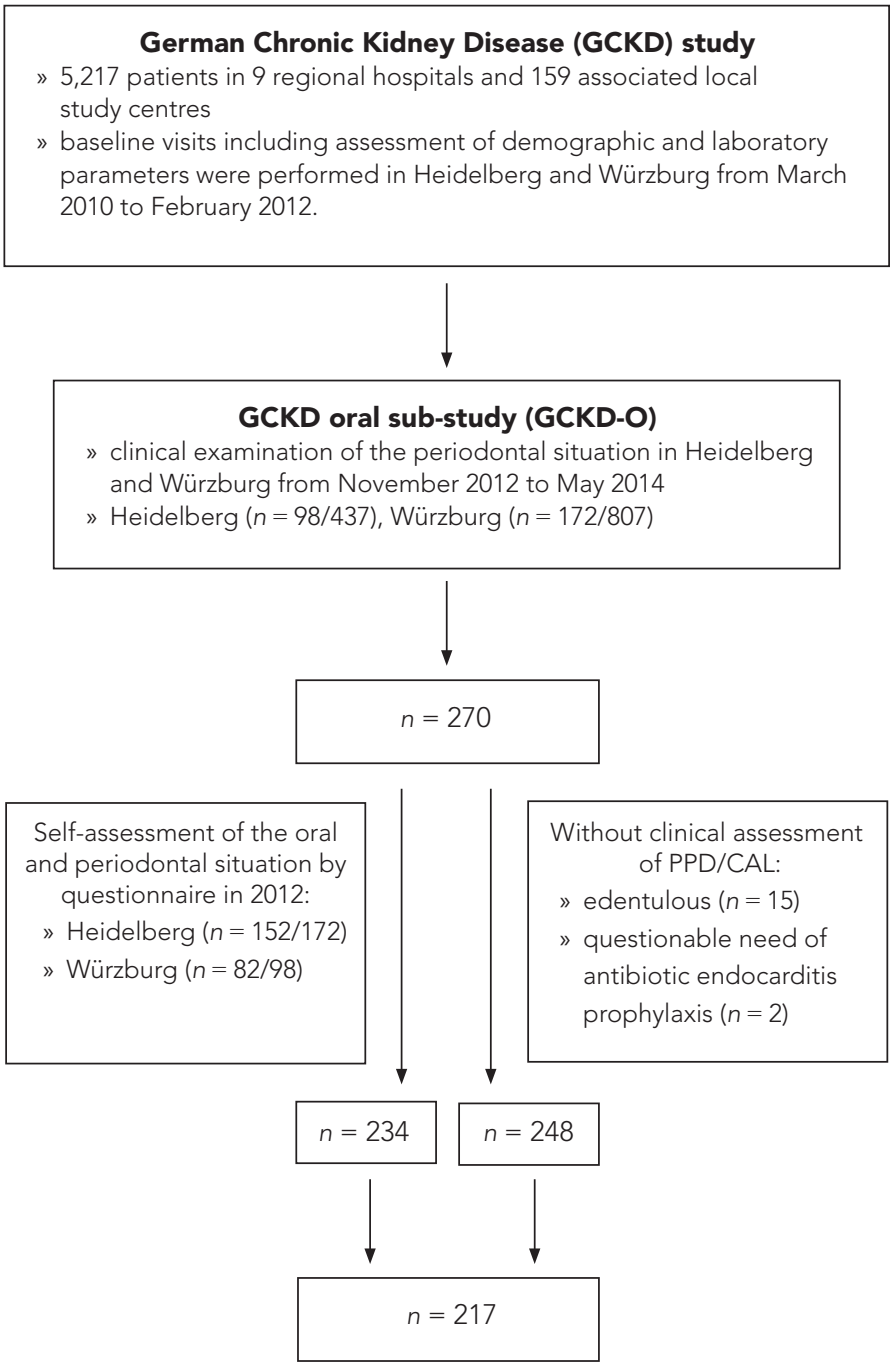

FIGURE 1 Flow chart displaying the process of patient selection and design of the GCKD-Oral

TABLE 1 Baseline characteristics and renal function of all GCKD-study participants in comparison with the GCKD-O cohort

	GCKD	GCKD-O	*p*
N (% of patients)	4,969 (95.2)	248 (4.8)	
Age, mean (*SD*)	60.1 (12.0)	60.1 (10.5)	n.s.[c]
Male sex (%)	2,974 (59.9)	158 (63.7)	n.s.[b]
Diabetes (%)	3,202 (64.4)	162 (65.3)	n.s.[b]
Non-smoker (%)	2,033 (41.0)	98 (39.7)	n.s.[b]
eGFR (ml/min/1.73 m^2), mean (*SD*)	47.2 (16.9)	44.4 (13.3)	.021[c]
eGFR stratified by CKD stages (KDIGO)			
G1/G2	809 (16.5)	29 (11.7)	n.s.[b]
G3a	1,672 (34.0)	79 (31.9)	
G3b	1,931 (39.3)	114 (46.0)	
G4	501 (10.2)	26 (10.5)	
ACR (mg/g), median (IQR)	52.9 (9.8–376.4)	67.3 (11.5–489.1)	n.s.[a]
CRP (mg/L), median (IQR)	2.3 (1.0–5.0)	2.2 (0.9–4.6)	n.s.[a]

Abbreviations: ACR, urine albumin-to-creatinine ratio; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate (MDRD4); KDIGO, kidney disease improving global outcome; n.s., not significant; *SD*, standard deviation.
[a]Mann–Whitney *U* test.
[b]Fisher's exact test/qui-square test.
[c]Student's *t* test.

Based on the probing data, each study patient was assigned to one of three different severity levels of periodontitis as defined by the joint working group of the Centers for Disease Control and Prevention and the American Academy of Periodontology (CDC/AAP) (Eke, Page, Wei, Thornton-Evans, & Genco, 2012). Additionally, the inflammatory load attributable to the observed periodontal disease was calculated using the periodontal inflamed surface area index (PISA) as described before (Nesse et al., 2008). PISA quantifies the amount of inflamed periodontal tissues in mm^2 by combining the recorded parameters PPD, CAL and BOP. As BOP is a parameter associated with active inflammation (Lang, Joss, Orsanic, Gusberti, & Siegrist, 1986), PISA may be used to distinguish subjects with an active inflammatory load from those with non-active inflammatory status in a quantitative manner.

2.4 | Statistical analysis

Descriptive analyses of patient characteristics were calculated as appropriate, and comparisons between groups were made using parametric or non-parametric tests for continuous variables. Categorical data were reported as percentages and compared by Fisher's exact test. One-way analysis of variance (ANOVA) was used to compare quantitative parameters among the study groups.

For self-reported items sensitivity, specificity, positive and negative predictive values (PPVs and NPVs) were determined for the discrimination of moderate/severe periodontitis versus no/mild periodontitis (disease categories were merged to two classes). We considered a measure to have good validity when the sum of PPV and NPV was 120% or above. This value was described before in the literature but is arbitrarily chosen (Blicher, Joshipura, & Eke, 2005). Statistical analyses were performed with SPSS version 24.0 (SPSS Inc.).

3 | RESULTS

3.1 | Compliance, dropouts

Figure 1 shows a flow chart of the recruitment process. A total of 1,244 patients were enrolled in the GCKD study at Heidelberg (*n* = 437) and Würzburg (*n* = 807) and completed the baseline visit. Two hundred seventy patients were consecutively enrolled for the dental clinical examination (Würzburg *n* = 172 and Heidelberg *n* = 98). Due to the need for antibiotic endocarditis prophylaxis before dental procedures, PPD/CAL was not measured in two patients. Twenty patients were edentulous, resulting in 248 patients with a complete, clinically assessed periodontal status. In 234 patients, data from the questionnaire and clinical evaluation were available.

3.2 | Patients' characteristics of the GCKD-study participants compared with the GCKD-O cohort

In Table 1, baseline characteristics of the total GCKD-study population (*n* = 5,217) versus the GCKD-O subpopulation demographics (*n* = 248) are listed. There were no significant differences between the total GCKD population when compared to the GCKD-O subjects regarding age, sex, diabetes, smoking habits, eGFR stratified by CKD stages, ACR and CRP values. Only the eGFR level was significantly higher ($p = .021$) in the total GCKD population (47.2 ± 16.9 ml/min/1.73 m^2) than in the GCKD-O subpopulation (44.4 ± 13.3 ml/min/1.73 m^2).

3.3 | Patients' characteristics stratified by CKD stage

A summary of the patients' demographic and clinical characteristics stratified by CKD stage is presented in Table 2. The mean age of the study population (*n* = 248) at baseline was 60.1 ± 10.5 years and varied significantly by GCKD stage, with the youngest patients in stage G1/G2 (53.6 ± 12.7 years) and the oldest ones in stage G4 (62.2 ± 11.4 years), 63.7% were male, 34.7% diabetics and 39.5% classified as non-smoker. There were no significant differences regarding gender, diabetes or smoking habits between patients in different CKD stages. The mean eGFR and median ACR were 44.4 ml/min/1.73 m^2 and 67.3 mg/g, respectively. Renal function

TABLE 2 Baseline characteristics of study participants by CKD stages

		eGFR stratified by CKD stages (KDIGO)				
	GCKD-O	G1/G2	G3a	G3b	G4	*p*
N (% of patients)	248	29 (11.7)	79 (31.9)	114 (46.0)	26 (10.5)	
Age (years), mean (*SD*)	60.1 (10.5)	53.6 (12.7)	60.5 (9.3)	61.0 (9.9)	62.2 (11.4)	.004[d]
Male sex (%)	158 (63.7)	16 (55.2)	50 (63.3)	80 (70.2)	12 (46.2)	n.s.[c]
Diabetes (%)	86 (34.7)	7 (24.1)	25 (31.6)	43 (37.7)	11 (42.3)	n.s.[c]
Non-smoker (%)	98 (39.5)	14 (48.3)	34 (43.0)	38 (33.6)	12 (46.2)	n.s.[c]
eGFR (ml/min/1.73 m^2), mean (*SD*)	44.4 (13.3)	70.8 (11.1)	50.4 (4.4)	37.7 (3.8)	26.0 (2.4)	<.001[d]
ACR (mg/g), median (IQR)	67.3 (11.5–489.1)	278.1 (29.0–1053.9)	52.4 (6.6–440.3)	62.9 (10.7–362.4)	51.9 (12.6–610.8)	n.s.[c]
Albuminuria (ACR) categories (%)						
A1 (<30 mg/g)	93 (37.5)	7 (24.1)	31 (39.2)	44 (38.6)	11 (42.3)	
A2 (30–300 mg/g)	82 (33.1)	9 (31.0)	26 (32.9)	40 (35.1)	7 (26.9)	
A3 (>300 mg/g)	73 (29.4)	13 (44.8)	22 (27.8)	30 (26.3)	8 (30.8)	
CRP (mg/L), median (IQR)	2.2 (0.9–4.6)	1.6 (0.5–5.6)	1.8 (0.9–4.4)	2.8 (1.3–6.3)	2.9 (1.1–10.1)	.016[b]
Number of teeth mean (*SD*)[a]	19.2 (8.0)	23.9 (5.1)	20.6 (7.0)	17.6 (8.2)	16.7 (9.8)	<.001[d]
PPD (mm), median (IQR)	2.4 (1.8–2.9)	2.0 (01.6–2.5)	2.3 (1.8–2.8)	2.5 (1.9–2.9)	2.6 (1.9–3.1)	.019[b]
PPD ≥ 6 mm (%), median (IQR)	0 (0–1)	0 (0–0.3)	0 (0–1.5)	0 (0–0.6)	0 (0–0)	n.s.[b]
BOP (%), median (IQR)	12.2 (2.3–26.3)	5.8 (0.6–10.6)	10.0 (1.8–19.7)	14.3 (2.7–32.2)	16.7 (8.4–34.5)	.002[b]
PISA (mm^2), median (IQR)	87.3 (15.3–226.1)	38.6 (5–137.5)	67.4 (20.4–273.6)	106.7 (15.4–228.3)	124.8 (33.3–235.4)	n.s.[b]
Patients in the highest PISA quartile (%)	62 (25.0)	4 (13.8)	22 (27.8)	30 (26.3)	6 (23.1)	n.s.[c]

Abbreviations: AAP, American Academy of Periodontology; ACR, urine albumin-to-creatinine ratio; BOP, bleeding on probing; CDC, Centers for Disease Control and Prevention; CKD, chronic kidney disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate (MDRD4); KDIGO, kidney disease improving global outcome; n.s., not significant; *SD*, standard deviation; PISA, periodontal inflamed surface area; PPD, probing pocket depth.

[a]Excluding third molars.

[b]Kruskal–Wallis test.

[c]Fisher's exact test/qui-square test.

[d]ANOVA.

was classified as stage G1/G2 in 11.7% of the patients, stage G3a in 31.9%, stage G3b in 46.0% and stage G4 in 10.5%. According to the NICE guidance, 118 participants (47.6%) of the GKD-O cohort were in the very high-risk category, 83 patients (33.5%) had a high risk, 40 subjects (16.1%) had a moderately increased risk, and seven patients (2.8%) had a low risk for adverse outcome and progression of CKD (Table 3). Demographic and clinical characteristics varied by CKD stage, with CKD stage G4 patients being more likely to be older, female, and display a higher frequency of diabetes relative to the other stages (Table 2). Displaying a significant increase in missing teeth with the loss of renal function (G1/G2: 23.9 vs. G4: 16.7, $p < .001$), the mean number of remaining teeth was 19.2 (excluding third molars). The median values for PPD and BOP increased significantly at higher CKD stages. According to the CDC/AAP case definition, 24.4% of the examined patients were categorized as periodontally healthy or mild periodontitis, 47.6% as moderate periodontal disease and 27.0% as severe periodontitis (Table 3 and 4). The prevalence of moderate and severe periodontitis was higher in CKD stage G3a (82.3%), stage G3b (75.4%) and stage G4 (69.2%) than in stage G1/2 (55.2%; no/mild vs. moderate/severe periodontitis, $p = .034$). Median PISA values tended to increase with the severity of CKD stages (38.6 mm^2 in stage G1/G2 to 124.8 mm^2 in stage G4), but the difference failed to reach the level of statistical significance (Table 2).

3.4 | Patients' characteristics of GCKD-O study participants stratified by severity of periodontal disease

In addition to the CKD stages, demographic and clinical characteristics varied by periodontitis category, with severe periodontitis patients being more likely to be older, male, displaying a higher frequency of diabetes and a lower number of non-smokers (Table 4). The values of eGFR, UACR and CRP did not differ significantly between periodontitis categories. Prognosis and risk for disease progression were further classified according to the NICE guidance. The results demonstrated only minor and inconsistent differences between periodontal disease categories (Table 3).

TABLE 3 Prognosis of CKD by GFR and albuminuria categories stratified for severity of periodontal disease according to the NICE guidance for early identification and management of CKD in adults (Carville et al., 2014)

	Albuminuria category			
CKD stages (KDIGO)	A1	A2	A3	GCKD-O
G1/G2 (%)	No/mild: 3 Moderate: 3 Severe: 1	No/mild: 4 Moderate: 2 Severe: 3	No/mild: 6 Moderate: 5 Severe: 2	No/mild: 13 (44.8) Moderate: 10 (34.5) Severe: 6 (20.7)
G3a (%)	No/mild: 2 Moderate: 16 Severe: 13	No/mild: 5 Moderate: 13 Severe: 8	No/mild: 7 Moderate: 13 Severe: 2	No/mild: 14 (17.7) Moderate: 42 (53.2) Severe: 23 (29.1)
G3b (%)	No/mild: 10 Moderate: 24 Severe: 10	No/mild: 11 Moderate: 15 Severe: 14	No/mild: 7 Moderate: 16 Severe: 7	No/mild: 28 (24.6) Moderate: 55 (48.2) Severe: 31 (27.2)
G4 (%)	No/mild: 3 Moderate: 4 Severe: 4	No/mild: 3 Moderate: 3 Severe: 1	No/mild: 2 Moderate: 4 Severe: 2	No/mild: 8 (30.8) Moderate: 11 (42.3) Severe: 7 (26.9)
GCKD-O	No/mild: 18 (19.4) Moderate: 47 (50.5) Severe: 28 (30.1)	No/mild: 23 (28.0) Moderate: 33 (40.2) Severe: 26 (31.7)	No/mild: 22 (30.1) Moderate: 38 (52.1) Severe: 13 (17.8)	

	Periodontitis category (CDC/AAP)			
	No/mild	Moderate	Severe	GCKD-O
Low risk (%)	3 (4.8)	3 (2.5)	1 (1.5)	7 (2.8)
Moderately increased risk (%)	6 (9.5)	18 (15.3)	16 (23.9)	40 (16.1)
High risk (%)	21 (33.3)	42 (35.6)	20 (29.9)	83 (33.5)
Very high risk (%)	33 (52.4)	55 (46.6)	30 (44.8)	118 (47.6)

Abbreviations: AAP, American Academy of Periodontology; ACR, urine albumin-to-creatinine ratio; CDC, Centers for Disease Control and Prevention; CKD, chronic kidney disease; KDIGO, kidney disease improving global outcome; NICE, National Institute for Health and Care Excellence. Colour code: green: low risk; yellow: moderately increased risk; orange: high risk; red: very high risk.

TABLE 4 Demographic, renal and periodontal characteristics by periodontitis category (CDC/AAP)

		Periodontitis category (CDC/AAP)			
	All	No/mild	Moderate	Severe	*p*
N (% of patients)	248	63 (24.4)	118 (47.6)	67 (27.0)	
Age, mean (*SD*)	60.1 (10.5)	55.6 (11.7)	61.4 (9.9)	62.1 (9.0)	.000[d]
Male Sex (%)	158 (63.7)	33 (52.4)	76 (64.4)	49 (73.1)	.05[c]
Diabetes (%)	86 (34.7)	18 (28.6)	39 (33.1)	29 (43.3)	n.s.[c]
Non-smoker (%)	98 (39.5)	27 (42.9)	51 (43.2)	20 (29.9)	n.s.[c]
eGFR (ml/min/1.73 m^2), mean (*SD*)	44.4 (13.3)	47.0 (17.3)	43.7 (12.1)	43.1 (10.6)	n.s.[d]
ACR (mg/g), median (IQR)	67.3 (11.5–489.1)	80.4 (12.9–793.3)	71.7 (8.8–453.3)	45.9 (12.2–242.6)	n.s.[b]
CRP (mg/L), median (IQR)	2.2 (0.9–4.6)	2.6 (1.1–5.9)	1.9 (1–5.7)	1.6 (0.8–3.7)	n.s.[b]
Number of teeth, mean (*SD*)[a]	19.2 (8.0)	19.2 (10.1)	19.2 (7.3)	18.4 (7.0)	n.s.[d]
BOP (%),median (IQR)	12.2 (2.3–26.3)	1.2 (0–8)	10.9 (3.9–18.5)	28.2 (14.8–45.8)	<.001[b]
PPD (mm), median (IQR)	2.4 (1.8–2.9)	1.9 (1.6–2.2)	2.3 (1.8–2.7)	3.0 (2.4–3.3)	<.001[b]
PISA (mm^2), median (IQR)	87.3 (15.3–226.1)	9.5 (0–28.3)	87.3 (24.3–167)	318.4 (149.1–520)	<.001[b]

Abbreviations: AAP, American Academy of Periodontology; ACR, urine albumin-to-creatinine ratio; BOP, bleeding on probing; CDC, Centers for Disease Control and Prevention; CKD, chronic kidney disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; KDIGO, kidney disease improving global outcome; n.s., not significant; *SD*, standard deviation; PISA, periodontal inflamed surface area; PPD, probing pocket depth.
[a]In dentated subjects excluding third molars.
[b]Kruskal–Wallis test.
[c]Fisher's exact test/qui-square test.
[d]ANOVA.

TABLE 5 Self-reported symptoms related to CKD stratified for different stages of kidney diseases

		eGFR stratified by CKD stages (KDIGO)			
Item	**All**	**G1/G2**	**G3a**	**G3b**	**G4**
N (% of patients)	234	24 (10.3)	72 (30.8)	112 (47.9)	26 (11.1)
Have you noticed any mouth dryness or less salivation?	226				
Yes (%)	49 (21.7)	5 (20.8)	11 (15.9)	23 (21.5)	10 (38.5)
No (%)	177 (78.3)	19 (79.2)	58 (84.1)	87 (78.5)	16 (61.5)
Have you experienced any mouth soreness?	225				
Yes (%)	34 (15.1)	5 (20.8)	10 (14.7)	14 (13.1)	5 (19.2)
No (%)	191 (84.9)	19 (79.2)	58 (85.3)	93 (86.9)	21 (80.8)
Do you have a bad taste or taste disturbances?	224				
Yes (%)	17 (7.6)	1 (4.2)	9 (13.0)	5 (4.7)	2 (8.0)
No (%)	207 (92.4)	23 (95.8)	60 (87.0)	101 (95.3)	23 (92.0)
Do you have problems with chewing or swallowing?	224				
Yes (%)	25 (11.2)	4 (16.7)	8 (11.8)	11 (10.4)	2 (7.7)
No (%)	199 (88.8)	20 (83.3)	60 (88.2)	95 (89.6)	24 (92.3)
Have you noticed any changes in your tongue?	224				
Yes (%)	41 (18.3)	6 (25.0)	16 (23.5)	13 (12.3)	6 (23.1)
No (%)	183 (81.7)	18 (75.0)	52 (76.5)	93 (87.7)	20 (76.9)
Are you conscious of bad breath?	222				
Yes (%)	47 (21.2)	4 (16.7)	13 (19.1)	24 (22.4)	6 (21.2)
No (%)	175 (78.8)	20 (83.3)	55 (80.9)	83 (77.6)	17 (73.9)
Have you noticed bleeding of your gums?	227				
Yes (%)	50 (22.0)	9 (39.1)	16 (18.2)	20 (18.7)	5 (19.2)
No (%)	177 (78.0)	14 (60.9)	55 (62.5)	87 (81.3)	21 (80.8)

Abbreviations: BOP, bleeding on probing; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; KDIGO, kidney disease improving global outcome

3.5 | Self-reported oral symptoms stratified by CKD stage

Table 5 summarizes the results regarding oral symptoms by CKD category as obtained from the self-reported questionnaire (n = 234). Overall, the most common manifestations were mouth dryness/less salivation (21.7%) and the presence of malodour (21.2%). Although mouth dryness was more prevalent in patients with stage G4 CKD (38.5%), there were no distinct correlations at different stages of CKD.

3.6 | Utilization of dental service and self-assessment of periodontal/oral status

The results summarized in Table 6 refer to the self-reported oral and periodontal status of clinically examined patients (n = 217). The majority of these patients visited their dentist once a year for regular oral check-ups (81.9%). No statistically significant difference could be observed within the three periodontitis categories. However, patients affected by severe kidney disease (G4, n = 26) showed significantly different patterns in the utilization of dental care compared with those in other stages: only 65.4% of them sought regular dental attendance, 15.4% showed up irregularly, 11.5% showed up only in case of dental pain, and 7.7% reported that they did not make use of dental service.

Overall, 22.3% of patients were conscious of malodour, 11.4% noticed red and/or swollen gums, 23.6% observed bleeding gums, 39% noticed recession of the gingiva, 6.9% observed moving teeth, and 14.2% indicated that their teeth were loose (Table 6). Individuals with severe periodontitis reported these symptoms more often than patients with moderate, mild or no periodontal disease. The corresponding items showed good positive predictive values (PPVs) between 76% and 93% but presented only low negative predictive values (NPVs) between 24% and 30%.

Although 74.7% of patients were clinically affected by moderate or severe periodontitis, their self-awareness of periodontal or gum disease was only 20.8% overall and 37.7% for severe periodontitis. Furthermore, only 48.1% of patients with severe periodontitis reported that they were informed about the presence of periodontal problems by their dentists, and 44.4% had previous periodontal treatment. These items demonstrated good PPV and acceptable NPV, resulting in a sum that was more than 120%. The percentage of positive ratings of these questions increased significantly with pronounced disease severity (Table 6).

TABLE 6 Self-reported utilization of dental service and awareness of symptoms related to periodontitis in relation to clinically assessed periodontitis categories

Items	All	Periodontitis category (CDC/AAP)			Sensitivity[a] Specificity	PPV[a] NPV
		No/mild	Moderate	Severe		
N (% of patients)	217	55 (25.3)	105 (48.4)	57 (26.3)		
Utilization of dental care	210					
Regular dental check-ups—at least once a year (%)	172 (81.9)	42 (79.2)	85 (84.2)	45 (80.4)		
Irregular dental check-ups (%)	18 (8.6)	6 (11.3)	8 (7.9)	4 (7.1)		
Visits only in case of dental pain (%)	17 (8.1)	4 (7.5)	7 (6.9)	6 (10.7)		
Never (%)	3 (1.4)	1 (1.9)	1 (1.0)	1 (1.8)		
Do you regularly make use of professional tooth cleaning?	208					
Yes (%)	118 (56.7)	27 (50.9)	64 (63.4)	27 (50.0)		
No (%)	90 (43.3)	26 (49.1)	37 (36.6)	27 (50.0)		
Are you conscious of bad breath?	206					
Yes (%)	46 (22.3)	11 (20.8)	21 (21.0)	14 (26.4)	23%	76%
No (%)	160 (77.7)	42 (79.2)	79 (79.0)	39 (77.7)	79%	26%
Are your gums red and/or swollen?	211					
Yes (%)	24 (11.4)	4 (7.5)	9 (8.7)	11 (20.0)	13%	83%
No (%)	187 (88.6)	49 (92.5)	94 (91.3)	44 (80.0)	93%	26%
Have you noticed any bleeding from your gums?	212					
Yes (%)	50 (23.6)	14 (26.4)	20 (19.4)	16 (28.6)	23%	72%
No (%)	162 (76.4)	39 (73.6)	83 (80.6)	40 (71.4)	74%	24%
Have your gums receded or have you noticed that you have more food impaction in the inter-dental areas?	205					
Yes (%)	80 (39.0)	14 (27.5)	40 (40.8)	26 (53.6)	43%	83%
No (%)	125 (61.0)	37 (72.5)	58 (59.2)	30 (46.4)	73%	30%
Have you noticed that your teeth moved position?	204					
Yes (%)	14 (6.9)	1 (2.0)	6 (6.0)	7 (12.7)	8%	93%
No (%)	190 (93.1)	48 (98.0)	94 (94.0)	48 (87.3)	98%	25%
Do you think that your teeth are loss or wobbly?	204					
Yes (%)	29 (14.2)	4 (8.2)	13 (13.1)	12 (21.4)	16%	86%
No (%)	175 (85.8)	45 (91.8)	86 (86.9)	44 (78.6)	92%	26%
Do you think that you have periodontal or gum disease?	202					
Yes (%)	42 (20.8)	8 (15.7)	14 (14.3)	20 (37.7)	23%	81%
No (%)	160 (79.2)	43 (84.3)	84 (85.7)	33 (62.3)	84%	66%
Have you ever been told by a dentist that you have periodontal or gum disease?	206					
Yes (%)	68 (33.0)	6 (11.3)	34 (34.3)	28 (48.1)	41%	91%
No (%)	138 (67.0)	47 (88.7)	65 (65.7)	26 (51.9)	89%	67%
Have you ever had any form of periodontal or gum treatment?	207					
Yes (%)	73 (35.3)	9 (17.0)	40 (40.0)	24 (44.4)	42%	88%
No (%)	134 (64.7)	44 (83.0)	60 (60.0)	30 (55.6)	83%	73%

Abbreviations: AAP, American Academy of Periodontology; CDC, Centers for Disease Control and Prevention; NPV, negative predictive value; n.s., not significant; PPV, positive predictive value.

[a]Discrimination of moderate/severe periodontitis vs. no/mild periodontitis.

4 | DISCUSSION

This cross-sectional study of a German population with moderate CKD revealed an overall prevalence of 47.6% for moderate and 27% for severe periodontitis according to the CDC/AAP criteria. The prevalence of moderate and severe periodontitis varied significantly by CKD stage. Overall, only 24.4% of enrolled patients were classified as periodontally healthy or with mild periodontitis. Bad breath, changes in the tongue and mouth dryness were the most common self-reported problems rated positively by approximately 20% of the participants.

The vast majority (81.9%) of responders reported visiting the dentist regularly at least once a year, and 73.7% had a dental check-up within the past 12 months. About half of the patients (51.9%) graded with severe periodontitis were never informed by their dentist that they suffered from gum disease, and only 44.4% stated that they received any form of periodontal therapy in the past.

Different clinical parameters may be used to define periodontal disease or the impairment of renal function. Thereby, study results evaluating the association between CKD and periodontal inflammation differ depending on the chosen parameters. Whereas trials evaluating the renal clearance by the assessment of serum cystatin C or iohexol filtration markers (GFR) generally found an association between CKD and periodontitis (Thorman, Neovius, & Hylander, 2009; Yoshihara, Iwasaki, Miyazaki, & Nakamura, 2016), studies analysing creatinine based on eGFR rate came to conflicting results (Grubbs et al., 2015; Tadakamadla, Kumar, & Mamatha, 2014; Wangerin et al., 2019). In this investigation, kidney function was assessed by the KDIGO clinical practice guideline, which is better suited for clinical trials than the standard CKD stage classification, used in previous studies. Furthermore, we analysed the impact of persistent albuminuria categories (A1, A2, A3) which are essential risk indicators of CKD progression.

Deschamps-Lenhardt (Deschamps-Lenhardt et al., 2019) conducted a specific meta-analysis including only studies with precise diagnostic. They observed an ascending trend of an association between CKD and moderate-to-severe periodontitis and recommend to determine the periodontal profile more precisely. This is in line with findings in our study. Similar to our study design, Sharma et al. described the prevalence of periodontitis in CKD patients enrolled in the Renal Impairment In Secondary Care (RIISC) study according to the CDC/AAP criteria. They observed a significantly higher prevalence of severe periodontitis (51.7%) at baseline (Sharma et al., 2014). However, most subjects included in this study had CKD stage G4 or 5 (68%) and only 24% had stage G3. In contrast, the GCKD study predominantly addressed individuals with moderate CKD (77.9% with stage G3) who did not require renal replacement therapy, and the patients were younger than in the RIISC study (60.1 vs. 63 years).

Iwasaki and co-workers reported an association between PISA and the incidence of decreased kidney function in a cohort of individuals aged 75 years in Japan. Patients in this study were classified into quartile groups according to PISA, and the highest quartile was compared with the other three groups combined. Subjects in the highest PISA quartile had an adjusted OR of 2.24 (95% CI, 1.05–4.79) for the progression of CKD (Iwasaki et al., 2012). In the present cohort, 25% of patients were in the highest quartile of PISA (≥226.1 mm^2) and would be at a higher risk of disease progression according to Iwasaki et al.

In addition to a clinical examination of oral status, the presence of periodontitis and related symptoms were evaluated by self-report. The items included in this questionnaire had shown high validity relative to clinical assessments in previous studies (Blicher et al., 2005; Dietrich et al. 2007; Genco, Falkner, Grossi, Dunford, & Trevisan, 2007; Gilbert & Nuttall 1999). CKD has well-documented effects on oral tissues, including xerostomia, taste disturbance, tongue coating, increased dental calculus and mucosal inflammation (Akar, Akar, Carrero, Stenvinkel, & Lindholm, 2011; Craig, 2008; Davidovich, Davidovits, Eidelman, Schwarz, & Bimstein, 2005; Proctor, Kumar, Stein, Moles, & Porter, 2005). Therefore, patients were also asked to report the possible oral effects of CKD. Overall, bad breath, changes in the tongue and mouth dryness were the most common problems rated positively by approximately 20% of the participants. However, no statistically significant differences between different CKD stages and the incidence of oral changes could be detected.

The vast majority (81.9%) of respondents reported visiting the dentist regularly at least once a year, and 73.7% had a dental check-up within the past 12 months. The patients graded with severe periodontitis showed a comparable attendance pattern (80.2% for regular dentist visits and 70.1% for a check-up within the past 12 months); 51.9% were never informed by their dentist that they suffered from gum disease, and only 44.4% stated that they received any form of periodontal therapy in the past. The self-reported presence of periodontal disease or recollection of being diagnosed or receiving treatment for periodontal disease demonstrated good PPVs and acceptable NPVs.

There is substantial evidence that periodontal disease induces a state of systemic inflammation (D'Aiuto, Nibali, Parkar, Suvan, & Tonetti, 2005; Hajishengallis, 2015; Paraskevas, Huizinga, & Loos, 2008; Tonetti, Van Dyke, & Working group 1 of the Joint, 2013), and previous studies have indicated that periodontitis contributes to the chronic systemic inflammatory burden associated with CKD (Nadeem, Stephen, Schubert, & Davids, 2009; Rahmati, Craig, Homel, Kaysen, & Levin, 2002). Serval reviews have confirmed systemic inflammation as an independent risk factor for the development and progression of CKD (Akchurin & Kaskel, 2015; Carrero & Stenvinkel, 2009). Moreover, the main cause of death in patients with CKD is cardiovascular events, which are directly related to the severity of kidney disease and an increased systemic inflammatory status (Gansevoort et al., 2013; Go et al., 2004). Periodontitis may therefore act as a comorbid inflammatory disease in patients with CKD by promoting the development of CVD, thereby contributing to an increased mortality rate (Kshirsagar et al., 2009; Sharma, Dietrich, Ferro, Cockwell, & Chapple, 2016). CKD shares many risk factors with periodontitis, such as diabetes mellitus, declining age and smoking. The overall prevalence of diabetes in the GCKD cohort was 34.7%. The proportion of individuals affected by diabetes at baseline rised consistently with the severity of kidney disease and periodontal disease. Patients with diabetes mellitus showed a statistically significant increased median PISA value compared to participants without diabetes (129.9 vs. 65.7 mm^2, $p = .036$).

A limitation of the study is the time frame between the data gathering of the dental and the renal parameters. As the baseline kidney parameters were assessed before the dental examination, there might be a bias in the data collections. But as both diseases are chronic processes, we suppose that the renal function parameters used in this study might be underestimated. As the present analysis is cross-sectional, only a non-directional association could

be assessed. A direct relation might be verified with prospective data in the further study course.

Our results indicate a high prevalence of periodontitis and periodontal treatment need in GCKD patients despite regular dental care. Even if the interactions between periodontal disease and CKD are not fully understood, periodontitis is a modifiable and effectively manageable health problem.

Considering the high prevalence of both diseases and the far-reaching consequences, disease programmes for patients suffering from CKD should include regular oral/periodontal status control for the early diagnosis and treatment of periodontitis. Future studies should analyse the amount of periodontal inflammation by assessing a full periodontal status with PPD, BOP and PISA on every tooth instead of using a partial or summarizing score. Furthermore, trials evaluating patients with moderate chronic kidney disease, who do not require renal replacement therapy, may benefit from a consistent definition of kidney function damage based on the KDIGO clinical practice classification and documentation of persistent albuminuria categories (A1, A2, A3) being essential risk indicators of CKD progression.

CONFLICT OF INTEREST

The authors declare that they have no financial or other relationships that might lead to a conflict of interest.

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