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RESEARCH

Association between serum biomarkers and oral health status in children with chronic kidney disease: A cross-sectional study

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Abstract

Objectives The aim of this study was to investigate the association between serum biomarkers and oral health parameters in children with chronic kidney disease (CKD).

Materials and methods Serum hemoglobin, blood urea nitrogen, serum creatinine, calcium, parathormone, magnesium, and phosphorus levels were measured in 62 children with CKD aged between 4 and 17 years. Intraoral examinations of the patients were performed by two different pediatric dentists. Dental caries was assessed using the decayed-missing-filled-teeth (DMFT/dmft) indexes, and oral hygiene was assessed using the debris (DI), calculus (CI), and simplified oral hygiene (OHI-S) indexes. Spearman's *rho* coefficient and generalized linear modeling were used to examine the association between serum biomarkers and oral health parameters.

Results The results of the study showed that there were negative and statistically significant correlations between serum hemoglobin and creatinine levels and dmft scores in pediatric patients with CKD ($p = 0.021$ and $p = 0.019$, respectively). Furthermore, blood urea nitrogen levels and DI and OHI-S scores ($p = 0.047$ and $p = 0.050$, respectively); serum creatinine levels and DI, CI, and OHI-S scores ($p = 0.005$, $p = 0.047$, $p = 0.043$, respectively); and parathormone levels and CI and OHI-S scores ($p = 0.001$ and $p = 0.017$, respectively) were found to be positively and statistically significantly related.

Conclusions There are associations between various serum biomarker levels and dental caries and oral hygiene parameters in pediatric patients with CKD.

Clinical relevance The impact of changes in serum biomarkers on oral and dental health is important for dentists' and medical professionals' approaches to patients' oral and systemic health.

Keywords Biomarkers · Chronic kidney disease · Dental calculus · Dental caries · Oral hygiene

Introduction

Chronic kidney disease (CKD) is a syndrome with a multitude of symptoms resulting from a permanent reduction in the number of nephrons or their permanent damage [1]. CKD is diagnosed based on structural or functional impairment of renal function and/or reduction of glomerular filtration rate to less than 60 mL/min/1.73 m^2, lasting more than three months [1]. The prevalence of CKD in children varies between 56 and 96 cases per million in European countries and between 15 and 74.7 cases per million worldwide [2, 3].

Various findings are observed in the craniofacial region and oral cavity of patients with systemic diseases and chronic conditions. Patients with CKD, whose life expectancy is getting longer with intensive treatments, transplantation and dialysis, are expected to present various oral symptoms at some point in their lives [4]. The effects of CKD on hard tissues in the craniofacial region include tooth discoloration, craniofacial growth distortions, an increase in dental debris, plaque, and calculus amount, a decrease in dental caries, developmental enamel defects, loss of teeth, bone fractures, and bone tumors [4–7]. CKD has effects on

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soft tissues such as xerostomia, hyposalivation, inflammation such as stomatitis and gingivitis, gingival hyperplasia due to medications such as cyclosporine, dysphagia, burning mouth sensation, and dysgeusia [4–7].

Creatinine is a metabolite that occurs as a result of the metabolism of phosphocreatine in the body to obtain the energy required for muscle function and is filtered in the kidney glomeruli before it is excreted in the urine [8]. Urea, which is a metabolite obtained from the nutritional protein and tissue protein cycles, is freely strained from the kidney glomeruli and reabsorbed by the renal tubules. The blood urea nitrogen level determined in serum is inversely proportional to the decrease in renal function and is affected by nutrition and various systemic factors [9]. Serum creatinine and blood urea nitrogen levels are the most widely used and acceptable indicators to evaluate the status of the disease and the effect of treatment in individuals with CKD [10, 11]. Apart from these two principal parameters, serum levels of hemoglobin, calcium, parathormone, magnesium, and phosphorus are also evaluated in the diagnosis, prognosis, management, and follow-up processes of patients with CKD [12].

Although an increase in the risk of dental caries is expected due to nutrition in patients with CKD who are recommended a relatively low protein and high carbohydrate diet regimen, it is known that the presence of highly buffered and alkaline saliva due to the elevated urea and phosphate concentrations is the cause of the lower caries observed in these patients [13]. Calcium burden increases in patients with CKD as a result of disturbances in the calcium-phosphate mechanism and the use of calcium-based phosphate binders [14, 15]. Elevated salivary pH, decreased salivary magnesium, and high levels of salivary urea and phosphate, probably due to the decrease in the glomerular filtration rate and urinary excretion, lead to the precipitation of calcium-phosphate and calcium oxalate and, thus, dental calculus formation [14, 15]. In patients with CKD, both dental caries and oral hygiene parameters are affected by disorders in systemic mineral metabolism and changes in salivary mineral levels as a result of medication use. Therefore, salivary biomarker levels may be a predictor of oral health [16]. On the other hand, there are certain limitations to using saliva as a diagnostic material. The use of saliva in patients with CKD has not become widespread due to disadvantages such as being affected by local inflammatory factors, requiring equipment and additional costs, and affecting the diagnosis by molecular size [16, 17].

Dentists encounter more children with CKD, given its global prevalence. On the other hand, considering the oral symptoms of patients with CKD and the need for dental treatment before kidney transplantation, medical professionals may encounter oral and dental problems in patients during the treatment and follow-up periods of patients with CKD [7]. Changes in serum biomarker levels provide insight into the development of various oral and dental symptoms related to the disease, as well as the process of the disease [4].

The aim of the study was to evaluate the association between serum biomarkers and dental caries and oral hygiene, which might give dentists foresight about the oral and dental health of pediatric patients with CKD just by looking at the blood tests ordered in their routine follow-up. The null hypothesis of the study was that there was no association between serum biomarkers and dental caries and oral hygiene status in children with CKD.

Methods

This study, which was approved by the Marmara University School of Medicine Clinical Research Ethics Committee with a protocol number of 09.2021.290, is a cross-sectional study, and the study was conducted in accordance with all ethical principles and obligations of the Declaration of Helsinki. The details of the study and the examination to be performed were explained to the patients with a suitable approach for their age, perception level, and decision-making capacity. After explaining the study to the patients, detailed information about the study was given to the parents and/or caregivers. For patients older than 7 years old, an informed consent form was signed by both the patient and their parents and/or caregivers. For patients younger than 7 years old, the informed consent form was signed by only their parents [18]. The study included 62 patients with CKD who were followed by the Pediatric Nephrology Unit, Pendik Research and Training Hospital of Marmara University, and applied to CKD outpatient clinics between April 2021 and April 2022. Patients included in the study were determined by the non-probability consecutive sampling method for cross-sectional studies. The diagnosis of CKD was defined according to the National Kidney Foundation guidelines [19]. According to these guidelines, CKD is defined as kidney damage lasting at least three months, characterized by structural and functional abnormalities of the kidney. This condition is detected by pathological abnormalities or markers of kidney damage, including abnormalities in blood and/or urine composition or abnormalities in imaging tests [19].

The inclusion criteria for the patients were that the patient was between the ages of 4 and 17, had been diagnosed with CKD in accordance with the National Kidney Foundation guidelines and criteria [19], did not have any co-morbid diseases and/or conditions (diabetes, hypertension, hyperlipidemia, cardiovascular diseases, smoking, obesity, and malnutrition) [20], did not undergo kidney transplantation, and had no periodontal treatment in the last six months [21].

In addition, patients who were diagnosed with CKD at least a year ago were included in the study [22].

Patients with CKD are routinely followed by pediatric nephrologists (SG, ÖNT, NÇ) with serum biomarkers such as hemoglobin (g/dl), blood urea nitrogen (g/dl), creatinine (mg/dl), calcium (mg/dl), parathormone (pg/ml), magnesium (mg/dl), and phosphorus (mg/dl) levels. No additional blood tests were requested from the patients for the study, and blood test results and demographic parameters were recorded from patient files. The patient's intraoral examination was performed on the same day as the CKD treatment follow-up session. Regardless of the study, routine blood test results were evaluated to assess the current status of the disease and treatment. In accordance with ethical responsibilities and obligations, the control group was not included in the study, since blood samples taken in the routine treatment follow-up sessions of CKD patients were evaluated and no blood samples would be taken from healthy peers.

Intraoral soft and hard tissue examinations were performed by two different pediatric dentists (NKD and RK). Prior to the study, examiners were trained by an experienced investigator (BS) in terms of intraoral findings in CKD. For the calibration of the examiners, fifteen patients were re-examined ten days after the first examination. After the week of calibration, the examiners collected the data on two occasions in a double-blind design. Intra- and inter-examiner agreement was tested using the intraclass correlation coefficient for quantitative parameters.

When performing the intraoral examination, the examiners used a headlamp (for illumination of the oral cavity during visual examination) and a standard plane-surface mouth mirror for visual examination, a standard dental probe for tactile examination and caries detection, and a standard millimeter-scale periodontal probe for periodontal examination.

In the evaluation of dental caries, the decayed-missing-filled-teeth (DMFT/dmft) indexes approved by the World Health Organization were used [23]. Capital letters (D, M, F, T) state the situation in permanent dentition; lowercase letters (d, m, f, t) state the situation in primary dentition. DMFT/dmft indexes are the most preferred indexes in clinical studies due to their advantages, such as being simple, valid, reliable, easy to use, and statistically useful [24].

The examination of the amount of dental calculus and debris, and oral hygiene was done using the Simplified Oral Hygiene Index (OHI-S). This index, approved and recommended by the World Health Organization, includes two sub-indexes: the Debris Index (DI) and the Calculus Index (CI) [23]. In permanent dentition, in reference to both indexes, the maxillary right central incisor (#11), maxillary right (#16) and left (#26) first molars, mandibular left central incisor (#31), and mandibular left (#36) and right (#46) first molars are evaluated. In the primary dentition, in reference to both indexes, the maxillary right central incisor (#51), maxillary right (#55) and left (#65) second molars, mandibular left central incisor (#71), and mandibular left (#75) and right (#85) second molars are evaluated. DI has four codes: code 0 = no debris, plaque, or stain on the tooth surface; code 1 = extrinsic stains without debris or plaque, or debris covering less than 1/3 of the tooth surface; code 2 = debris presence covering more than 1/3 of the tooth surface; code 3 = debris presence covering more than 2/3 of the tooth surface. CI also has four codes: code 0 = no dental calculus; code 1 = supragingival dental calculus presence covering less than 1/3 of the tooth surface; code 2 = supragingival dental calculus presence covering 1/3–2/3 of the tooth surface and/or flecks of subgingival dental calculus around the cervical area of the tooth; code 3 = supragingival dental calculus presence covering more than 2/3 of the tooth surface and/or a continuous heavy band of subgingival dental calculus around the cervical region of the tooth. The sum of the codes determined according to the debris and calculus level on the buccal and lingual/palatal surfaces of the reference teeth is divided by the total number of tooth surfaces explored. Thus, the DI and CI scores of the individual are determined. The OHI-S score, obtained as a result of the sum of the DI and CI scores of the individual, shows the oral hygiene status, and a decrease in this score means an improvement in the oral hygiene status [25].

The primary outcome of the study was to measure the relationship between blood urea nitrogen and serum creatinine levels and oral hygiene index scores. The secondary outcome of the study was to measure the relationship between other serum biomarker levels and oral health status.

Sample size calculation

G*Power 3.0.10 statistical software (v. 3.1.9.7, Universitat Kiel, Kiel, Germany) was used to calculate the sample size. Based on the data from Pham and Le's study [26], which found a statistically significant correlation between creatinine clearance and DMFT scores ($\beta = -0.02$, $p = 0.016$, and $R^2 = 0.18$), it was determined that the minimum sample size should be 54 to achieve correlation effect size IrI 0.424 and achieve power of 90% with significance level (α) set at 0.05 in order to perform correlation analysis in the bivariate normal model.

Statistical analysis

The data set was created by entering the demographic, medical, and dental data obtained from the patients into Microsoft Excel 2016 (Microsoft, Redmond, WA, USA). For statistical analysis using the Statistical Package for the Social Sciences (SPSS Version 26.0, IBM Corp., Chicago, IL, USA), data were analyzed for normality assumptions for the continuous variables using the Shapiro–Wilk test in the

Table 1 Intraclass correlation coefficients for inter- and intra-examiner agreement in oral health status indexes

	Inter-examiner		Intra-examiner			
			Examiner-1		*Examiner-2*	
	ICC	*95% CI*	*ICC*	*95% CI*	*ICC*	*95% CI*
DMFT/dmft	0.86	0.586–0.912	0.96	0.934–0.988	0.95	0.876–0.977
DI, CI, and OHI-S	0.87	0.546–0.956	0.95	0.924–0.978	0.92	0.912–0.976

DMFT/dmft: decayed-missing-filling-teeth, DI: Debris Index, CI: Calculus Index, OHI-S: Simplified Oral Hygiene Index, ICC: Intraclass correlation coefficient, CI: Confidence interval

same software program. Quantitative data are expressed as the mean ± standard deviation, median, and first and third quartile values. Spearman's correlation was used to determine the relationship between serum biomarker levels and oral health findings. After determining the serum biomarkers that have a statistically significant effect on oral health by correlation analysis, these variables were included in the generalized linear models. Although age and sex variables were included in all models, the hemoglobin explanatory variable was included in the dmft outcome variable model; the blood urea nitrogen explanatory variable was included in the DI and OHI-S outcome variable models; the serum creatinine explanatory variable was included in the dmft, DI, CI, and OHI-S outcome variable models; and the parathormone explanatory variable was included in the CI and OHI-S outcome variable models. p-values of less than 0.05 were considered statistically significant.

Results

For the intraoral examination, the intraclass correlation coefficient indicated excellent intra-examiner agreement (between 0.96 and 0.92) and good inter-examiner agreement (0.86 and 0.87, respectively) (Table 1). As a result of the statistically insignificant difference between the inter- and intra-examiner agreements, it showed that the intraclass correlation coefficient values were considerably strong and reliable.

A total of 62 patients with CKD (48.4% females and 51.6% males; age range: 4–17 years; mean age: 12.08 ± 4.09) were included in this study, and the collected data was analyzed. Table 2 shows the patients' demographic information. The mean hemoglobin level was 12.15 ± 1.96 g/dl, the mean blood urea nitrogen level was 38.36 ± 25.42 g/dl, the mean serum creatinine level was 3.74 ± 4.19 mg/dl, the mean calcium level was 9.68 ± 0.96 mg/dl, the mean parathormone level was 184.09 ± 191.81 pg/ml, the mean magnesium level was 2.36 ± 0.59 mg/dl, and the mean phosphorus level was 4.82 ± 1.29 mg/dl. The mean and standard deviation, median, and first and third quartile values of serum biomarker levels of the patients included in the study are shown in Table 3.

Table 2 Demographic data of the patients

	(mean ± SD)
Age	12.08 ± 4.09 (range: 4–17)
	N (%)
Sex	
Female	30 (48.4)
Male	32 (51.6)
Dentition type	
Permanent dentition	34 (54.8)
Mixed dentition	19 (30.6)
Primary dentition	9 (14.5)

N: number, SD: standard deviation

Table 3 Descriptive values of serum biomarker levels

	Mean	Median	Standard Deviation	Q1	Q3
Hemoglobin (g/dl)	12.15	12.35	1.96	11.10	13.50
Blood Urea Nitrogen (g/dl)	38.36	32.50	25.42	18.25	55.75
Serum Creatinine (mg/dl)	3.74	2.25	4.19	1.00	4.80
Calcium (mg/dl)	9.68	9.75	0.96	9.32	10.10
Parathormone (pg/ml)	184.09	124.00	191.81	54.05	264.75
Magnesium (mg/dl)	2.36	2.30	0.59	2.00	2.70
Phosphorus (mg/dl)	4.82	4.50	1.29	4.00	5.30

g: gram, dl: deciliter, mg: milligram, pg: picograms, ml: milliliter, Q1: first quartile, Q3: third quartile

Thirty-four (54.8%) of the patients in the study were in permanent dentition, 19 (30.6%) in mixed dentition, and 9 (14.5%) in primary dentition. When dental caries and oral hygiene parameters in different dentition types were evaluated, it was determined that DMFT/dmft, CI, and OHI-S scores were statistically significantly different between the groups (p = 0.043, p = 0.030, and p = 0.034, respectively) (Table 4). For all patients, the mean DMFT score was 1.07 ± 1.56, the mean dmft score was 1.67 ± 2.7, the mean DI score was 1.2 ± 0.56, the mean CI score was 0.53 ± 0.55, and the mean OHI-S score was 1.74 ± 0.99.

Table 4 Comparison of dental caries and oral hygiene indexes scores in different dentition types

	DMFT/dmft					DI				CI				OHI-S				
	Mean	Median	SD	Q1 Q3	p-value	Mean	Median	SD	Q1 Q3	p-value	Mean	Median	SD	Q1 Q3	p-value	Mean	Median	SD	Q1 Q3	p-value
Permanent dentition	1.43	1.00	1.70	0.002.50	**0.043**	1.33	1.33	0.54	1.00 1.66	0.05	0.69	0.66	0.61	0.08 1.00	**0.030**	2.03	1.83	1.03	1.25 2.83	**0.034**
Mixed dentition	1.84	1.00	2.06	0.003.50		1.12	1.16	0.54	0.83 1.42		0.31	0.33	0.36	0.00 0.50		1.43	1.33	0.79	1.00 1.83	
Primary dentition	2.13	0.00	4.16	0.001.50		0.85	0.92	0.56	0.54 1.25		0.33	0.17	0.43	0.00 0.54		1.18	1.16	0.83	0.79 1.67	

Bold values mean statistically significant ($p < 0.05$). DMFT/dmft: decayed-missing-filling-teeth, DI: Debris Index, CI: Calculus Index, OHI-S: Simplified Oral Hygiene Index, SD: Standard deviation, Q1: first quartile, Q3: third quartile

Table 5 Descriptive values of oral health indexes scores

	Mean	Median	Standard Deviation	Q1	Q3
DMFT	1.07	0.00	1.56	0.00	2.00
dmft	1.67	0.00	2.70	0.00	3.00
DI	1.20	1.16	0.56	0.87	1.62
CI	0.53	0.50	0.55	0.00	0.78
OHI-S	1.74	1.66	0.99	1.00	2.28

DMFT/dmft: decayed-missing-filling-teeth, DI: Debris Index, CI: Calculus Index, OHI-S: Simplified Oral Hygiene Index, Q1: first quartile, Q3: third quartile

The mean and standard deviation, median, and first and third quartile values of the DMFT/dmft, DI, CI, and OHI-S indexes of the patients included in the study are shown in Table 5.

As a result of the Shapiro–Wilk test for the normality of the data distribution, it was observed that the data were not normally distributed. For this reason, Spearman's *rho* correlation coefficient was used to determine the correlation relationship between the data. A statistically significant negative correlation was observed between hemoglobin levels and dmft scores ($r = -0.413$, $p = 0.021$). Statistically significant positive correlations were observed between blood urea nitrogen levels and DI and OHI-S scores ($r = 0.274$, $p = 0.021$; $r = 0.270$, $p = 0.023$, respectively). Positive correlations were also determined between serum creatinine levels and DI, CI, and OHI-S scores ($r = 0.259$, $p = 0.029$; $r = 0.296$, $p = 0.012$; $r = 0.313$, $p = 0.008$, respectively). In addition, a negative and statistically significant correlation was found between serum creatinine levels and dmft scores ($r = -0.419$, $p = 0.019$). Finally, statistically significant, positive correlations were observed between serum parathormone levels and CI and OHI-S scores ($r = 0.363$, $p = 0.002$; $r = 0.299$, $p = 0.011$, respectively). The results of the correlation analysis between serum biomarkers and oral health index scores are shown in Table 6.

Table 7 shows the generalized linear models that included the studied variables for defining factors that affected the oral health parameters. It was observed that the models were significant with all the variables included in the model for dmft, DI, CI, and OHI-S scores ($p = 0.001$, $p = 0.001$, $p = 0.001$, and $p = 0.003$, respectively). Hemoglobin ($p = 0.025$) and serum creatinine ($p = 0.036$) were significant factors affecting dmft scores. Blood urea nitrogen ($p = 0.047$) and serum creatinine ($p = 0.005$) were significant factors affecting DI scores. While serum creatinine ($p = 0.047$ and $p = 0.043$, respectively) and parathormone ($p = 0.001$ and $p = 0.017$, respectively) were significant factors affecting CI and OHI-S scores, blood urea nitrogen ($p = 0.050$) was also a significant factor affecting OHI-S scores.

Table 6 Correlation analysis results between serum biomarkers and oral health scores

		DMFT	dmft	DI	CI	OHI-S
Hemoglobin	*r-value*†	-0.095	-0.413	-0.160	-0.138	-0.173
	p-value†	0.458	**0.021**	0.184	0.250	0.150
Blood Urea Nitrogen	*r-value*†	0.060	-0.241	0.274	0.205	0.270
	p-value†	0.640	0.192	**0.021**	0.087	**0.023**
Serum Creatinine	*r-value*†	0.078	-0.419	0.259	0.296	0.313
	p-value†	0.542	**0.019**	**0.029**	**0.012**	**0.008**
Calcium	*r-value*†	-0.202	0.122	-0.155	-0.057	-0.146
	p-value†	0.112	0.514	0.195	0.636	0.224
Parathormone	*r-value*†	0.111	-0.182	0.163	0.363	0.299
	p-value†	0.386	0.328	0.175	**0.002**	**0.011**
Magnesium	*r-value*†	0.027	0.138	0.094	0.063	0.112
	p-value†	0.834	0.458	0.437	0.602	0.354
Phosphorus	*r-value*†	-0.077	-0.118	0.146	0.188	0.162
	p-value†	0.551	0.528	0.224	0.117	0.178

DMFT/dmft: decayed-missing-filling-teeth, DI: Debris Index, CI: Calculus Index, OHI-S: Simplified Oral Hygiene Index. The *p*-value defines the significance of the result of the correlation analysis between blood biomarker levels and oral health indexes scores. All values marked in bold are statistically significant ($p < 0.05$). †Spearman correlation analysis

Discussion

Although saliva has many advantages in collecting samples compared to blood [27], its use cannot be widespread due to some disadvantages [17]. It is not possible to detect of molecules of large weight and/or charged molecules in saliva, since these molecules cannot pass from plasma to saliva. In addition, many of the smaller molecules are present in saliva at significantly lower levels than in plasma. Oral hygiene status and habits of the individual, periodontal and gingival health, and the presence of gingival inflammation and bleeding may cause bias in saliva samples [17, 28]. The urease from oral microorganisms can affect the level of urea determined in saliva through local degradation of urea in oral cavity [29]. This suggests that microbiome patterns of the individual, as well as oral hygiene status, may affect the urea level and concentration measured in saliva and potentially other metabolites. Saliva urea concentrations are also affected by the time from collection to measurement [30]. The fact that the urea levels observed in saliva are lower than in blood can be considered a measure of the self-purifying efficiency of blood and saliva [31]. In addition, xerostomia, a frequently observed finding in CKD patients, causes problems with saliva collection [17]. Also, in underdeveloped and developing countries where clinical circulation is busy, issues such as the training of medical professionals on saliva collection, the need for additional equipment and cost, and adherence to traditional methods limit the detection of biomarkers from saliva samples. Considering all these, it should be kept in mind that serum biomarkers of CKD patients may be a predictor for oral health parameters during routine controls. Thus, with multidisciplinary cooperation, both the systemic and oral health of pediatric patients with CKD can be improved.

The changing concentration of metabolic products, minerals, and hormones in the bloodstream of CKD patients has been extensively discussed in the scientific literature. Hemoglobin is a protein inside erythrocytes that is involved in transporting oxygen to organs and tissues, and carrying carbon dioxide back to the lungs from organs and tissues [32]. Anemia, defined as a hemoglobin level of less than 12 g/dl, is a frequently observed problem in CKD patients in large-scale population studies [33]. North American Pediatric Renal Trials and Collaborative Studies showed that the prevalence of anemia in children with CKD ranged from 73 to 93% [34]. Human studies show an increased risk of early childhood caries in children with anemia [35–37]. Furthermore, animal studies have shown that anemic mice have a significantly higher risk of dental caries than nonanemic mice [38]. In the light of this information, the negative and statistically significant correlation observed between hemoglobin levels and dmft scores in this study is in line with the findings of these studies.

The blood urea nitrogen level, which is affected by renal tubular resorption and urea production as well as glomerular filtration, is inversely proportional to renal function and is one of the main parameters used to evaluate kidney function [39]. Studies have shown that blood urea nitrogen levels and salivary urea nitrogen levels are correlated [40]. The increase in salivary pH, and urea and phosphorus levels accelerate calcium-phosphate and calcium-oxalate precipitation and thus increase the accumulation of debris and dental calculus [14]. Davidovich et al. [14], who found statistically significantly more dental calculus formation in CKD

Table 7 Summary of generalized linear models predicting the oral health indexes scores

	dmft					DI					CI					OHI-S				
			95% Wald CI					95% Wald CI				95% Wald CI					95% Wald CI			
	B	*Std. error*	*Lower*	*Upper*	*p-value*	*B*	*Std. error*	*Lower*	*Upper*	*p-value*	*B*	*Std. error*	*Lower*	*Upper*	*p-value*	*B*	*Std. error*	*Lower*	*Upper*	*p-value*
Constant	2.358	5.630	- 13.392	8.675	**0.001**	0.924	0.232	0.470	1.379	**0.001**	0.640	0.194	- 0.241	0.522	**0.001**	1.137	0.385	0.383	1.892	**0.003**
Age	- 0.236	- 0.181	- 0.591	0.119	0.192	0.009	0.018	- 0.026	0.045	0.603	0.009	0.015	- 0.022	0.040	0.581	0.015	0.030	- 0.044	0.074	0.619
Sex[‡]	- 0.158	0.986	- 2.091	1.775	0.873	0.124	0.146	- 0.164	0.411	0.399	0.080	0.122	- 0.160	0.319	0.514	0.249	0.243	- 0.228	0.727	0.306
Hb	- 0.526	0.209	- 0.277	1.328	**0.025**															
BUN						0.124	0.034	- 0.005	0.456	**0.047**						0.313	0.067	- 0.013	0.654	**0.050**
SC	- 0.185	0.260	- 0.695	0.324	**0.036**	0.567	0.197	- 0.447	0.900	**0.005**	0.217	0.031	- 0.064	0.509	**0.047**	0.320	0.065	- 0.019	0.449	**0.043**
PTH											0.534	0.185	0.010	0.617	**0.001**	0.432	0.158	0.112	0.763	**0.017**

CI: Confidence Interval, Std.: Standard, dmft: decayed-missing-filling-teeth, DI: Debris Index, CI: Calculus Index, OHI-S: Simplified Oral Hygiene Index; B: unstandardized regression coefficient, Hb: Hemoglobin, BUN: Blood urea nitrogen, SC: Serum Creatinine, PTH: Parathormone. [‡]Reference: male. Bold values mean statistically significant ($p < 0.05$)

patients compared to the healthy individuals, stated that the reason for this situation was the increase in urea and oxalate concentrations in saliva due to decreased glomerular filtration rate and urinary excretion. Many studies have reported that individuals with CKD have more dental debris, plaque, and calculus formation than healthy individuals [7, 41–44]. The statistically significant relationship between blood urea nitrogen levels and DI and OHI-S scores in our study is also consistent with the results of these studies.

The serum level of creatinine, a large molecule with a high molecular weight and low lipid solubility, is elevated in CKD. In CKD patients, the increased serum creatinine level begins to diffuse into the saliva, creating a concentration gradient [45]. Although the mechanisms linking serum creatinine concentration to the state of periodontal and oral health have not yet been clarified [46], it has been reported that the formation of debris, plaque, and dental calculus is higher in CKD patients with elevated serum and salivary creatinine levels [7, 41–44]. Although the findings of our study are in parallel with the results of these studies, a negative and statistically significant correlation was also observed between serum creatinine levels and dmft scores in our study. It has been shown in many studies that individuals with CKD have less dental caries than their healthy peers [7, 13, 47]. It is known that in CKD patients, the risk of dental caries is reduced by neutralizing the end products of the bacterial plaque as a result of the increase in salivary pH due to urea hydrolysis [13]. However, there is no consensus in the scientific literature regarding the prevalence of dental caries in CKD patients. Therefore, although we found a negative and significant correlation between the dmft scores and serum creatinine levels, the fact that the DMFT score was not correlated with any serum biomarker supports this uncertainty.

Parathormone, which reflects the function of the parathyroid gland, primarily metabolizes calcium, phosphate, fibroblast growth factor 23, and vitamin D [48]. The number of studies investigating the increase in parathormone and thus the effects of hyperparathyroidism on oral health in patients with CKD is very few. In these studies [49, 50], parathormone levels and dental plaque and debris amount, periodontal pocket depth, and gingival bleeding level on probing were evaluated, and no significant correlation was observed between the parameters. In this study, statistically significant relationship was found between serum parathormone levels and CI and OHI-S scores. We think that this significant relationship may be due to the effects of parathormone on mineral metabolism, especially calcium and phosphate. Considering the negative and positive correlations between different serum biomarkers and oral health parameters, the null hypothesis of the study was partially rejected.

This study has some limitations. Some of these are the relatively small sample size, the fact that the nutritional and oral hygiene habits of the patients included in the study

were not evaluated, the results were not generalizable to all patients with CKD, the gingival and periodontal health was not evaluated in detail with different indexes, and the existence of other possible factors that may affect the patients' oral health. The absence of control group patients in the study is another limitation, since blood samples cannot be taken from healthy children due to ethical obligations. On the other hand, the use of easy-to-use indexes with validity and reliability, the fact that it is a multidisciplinary study, and the fact that intra- and inter-examiner agreement is ensured are the strengths of the study.

Conclusion

The results of this study show that there are significant associations between different serum biomarkers and oral health parameters in children with CKD. Considering the prevalence of the disease in the community and the intraoral findings specific to the disease, it is important for both dentists and medical professionals to evaluate serum biomarker levels in terms of oral health in the treatment and follow-up sessions. Although we think that the results of this study are important in this direction, we believe that these findings will shed light on future studies evaluating different serum biomarkers and different oral health parameters in larger sample groups.

Authors' contributions Conceptualization: [Berkant Sezer], [Harika Alpay], [Betül Kargül]; Methodology: [Berkant Sezer], [Harika Alpay], [Betül Kargül]; Formal analysis and investigation: [Berkant Sezer], [Nur Kodaman Dokumacıgil], [Remziye Kaya], [Serçin Güven], [Özde Nisa Türkkan], [Neslihan Çiçek]; Writing—original draft preparation: [Berkant Sezer]; Writing—review and editing: [Berkant Sezer], [Serçin Güven], [Özde Nisa Türkkan], [Neslihan Çiçek], [Harika Alpay], [Betül Kargül]; Supervision: [Harika Alpay], [Betül Kargül].

Data availability The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Competing interests The authors declare no competing interests.

Ethics approval This cross-sectional study was approved by the Clinical Research Ethical Committee of the School of Medicine, Marmara University with a protocol number of 09.2021.290. The study was conducted in accordance with all the ethical principles of the Declaration of Helsinki.

Consent to participate Patients included in the study and their parents or caregivers were informed about the study and signed informed consent forms.

Competing interest The authors declare no competing interests.

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