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Posted Date: 25 February 2026

doi: 10.20944/preprints202602.1299.v1

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Article

Oral–Systemic Interactions: Biomarkers, Inflammatory Pathways, and Disease Cross-Talk

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Abstract

Background and Objectives: The present study aimed to evaluate the association between dental caries, periodontal pockets, and radiologically detected periapical lesions with serum levels of Dickkopf-1 (Dkk-1) and tartrate-resistant acid phosphatase 5 (TRAP-5) in oncological patients with ear, nose, and throat (ENT) cancer compared with healthy controls. *Materials and Methods:* The study included 63 subjects divided into a study group of 33 patients diagnosed with ENT cancer and a control group of 30 healthy individuals. Blood samples were collected to determine serum Dkk-1 levels using a sandwich enzyme immunoassay and TRAP-5 levels. Dental radiological evaluation consisted of orthopantomography (OPT) and cone-beam computed tomography (CBCT) to assess the number and depth of dental caries and the presence of periapical lesions. Periodontal pockets were recorded through clinical examination. *Results:* OPT assessment showed a maximum of eight carious sites in both groups. The mean number of carious lesions was higher in healthy subjects (2.97 ± 2.48) than in cancer patients (2.06 ± 2.29). CBCT evaluation revealed 0–8 carious lesions in healthy individuals (maximum = 8) and 0–6 lesions in cancer patients (maximum = 6). The mean number of caries detected by CBCT was significantly higher in the control group (2.97 ± 2.48) compared with the cancer group (1.85 ± 1.89). Periodontal pockets were more frequent in cancer patients (mean: 0.67 ± 1.32) than in controls (0.37 ± 0.81). OPT evaluation showed a higher mean number of periapical lesions in cancer patients (0.82 ± 1.29) compared with controls (0.37 ± 0.67). CBCT examination demonstrated that the mean number of periapical lesions in cancer patients was more than twice that of the control group; however, this difference did not reach statistical significance. *Conclusions:* Patients with ENT cancer presented a higher prevalence of periodontal pockets and periapical lesions compared with healthy controls, while carious lesions were more frequently detected in healthy individuals. Radiological findings, together with systemic biomarkers such as Dkk-1 and TRAP-5, may contribute to a better understanding of oral–systemic interactions in oncological patients.

Keywords: periodontal pockets; dental caries; periapical lesions; cone-beam computed tomography; Dickkopf-1; TRAP-5; ENT cancer

1. Introduction

Dental caries is a biofilm-mediated, diet-modulated, multifactorial, non-communicable disease characterized by progressive mineral loss of dental hard tissues [1–3]. Its development is influenced by biological, behavioral, psychosocial, and environmental factors, ultimately leading to structural destruction of enamel and dentin [4]. Accurate diagnosis—based on clinical and radiographic evaluation—is essential for appropriate management and long-term disease control [5,6]. Contemporary caries management integrates primary, secondary, and tertiary preventive strategies under a comprehensive, risk-based approach [4,7].

Saliva plays a central protective role in maintaining enamel integrity and regulating demineralization–remineralization dynamics [8–11]. Conditions such as polypharmacy, Sjögren's syndrome, and radiotherapy for head and neck cancer may impair salivary gland function, increasing

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susceptibility to dental caries and erosion [12,13]. Dental caries and periodontitis are the leading causes of tooth loss worldwide and share common behavioral and socioeconomic risk factors [14–21]. However, their potential biological interrelationships and systemic implications remain incompletely elucidated [21–24].

Radiographic assessment is fundamental in detecting proximal and periapical pathology. Conventional bitewing radiographs identify approximately 60% of proximal lesions [25–28], while digital systems have not substantially improved detection rates [29–36]. Panoramic radiography provides broad anatomical visualization with greater patient comfort [29], whereas cone-beam computed tomography (CBCT) allows three-dimensional evaluation and has demonstrated diagnostic performance comparable to intraoral radiography in non-restored teeth [29,37–43].

Beyond local clinical parameters, systemic biomarkers may offer insight into oral–systemic interactions. Dickkopf-1 (Dkk-1), a Wnt signaling pathway inhibitor, regulates osteoblast differentiation and bone remodeling, and its dysregulation has been associated with inflammatory and neoplastic bone processes [44–49]. Tartrate-resistant acid phosphatase 5B (TRAP-5B) reflects osteoclast number and activity and is considered a reliable marker of bone resorption [50]. Alterations in these biomarkers may indicate systemic bone remodeling imbalance in inflammatory and oncologic conditions.

Radiation-related caries represents a severe complication in patients undergoing radiotherapy for head and neck cancer, resulting from salivary dysfunction, microbiota changes, mucosal alterations, and impaired oral hygiene [51]. Given the complex interaction between local oral pathology, systemic inflammation, and bone metabolism, investigating bone turnover biomarkers in oncologic patients may provide additional understanding of oral–systemic crosstalk.

Therefore, the aim of this study was to evaluate the association between dental caries, periodontal parameters, and radiologically detected periapical lesions with serum Dkk-1 and TRAP-5B levels in patients with ENT cancer compared with healthy controls.

2. Materials and Methods

2.1. Study Design and Sample Size

This case–control study evaluated the association between radiologically detected oral inflammatory lesions and systemic bone remodeling biomarkers in patients with head and neck (ENT) cancer.

A total of 63 participants were recruited between June and November 2021 from the Regional Institute of Oncology Iași and the "Grigore T. Popa" University of Medicine and Pharmacy of Iași. The study group included 33 patients with histopathologically and CT-confirmed head and neck cancer. The control group comprised 30 systemically healthy individuals.

Sample size was calculated using G*Power 3.1 (two-tailed t-test, $\alpha = 0.05$, power = 0.80). Based on an expected medium-to-large effect size (d = 0.75) derived from pilot observations, a minimum of 29 participants per group was required. The final sample exceeded this threshold.

The study was approved by the Ethics Committee of the "Grigore T. Popa" University of Medicine and Pharmacy of Iași (Approval No. 85/26.05.2021) and conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent.

2.2. Eligibility Criteria

Study Group

Inclusion criteria:

Age 24–80 years; histopathologically and CT-confirmed head and neck cancer; absence of distant metastases; no previous oncologic therapy; presence of dental pathology.

Exclusion criteria:

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Metastases; previous or ongoing radiotherapy/chemotherapy; age <24 or >80 years; absence of dental pathology.

Control Group

Inclusion criteria:

Age 24–80 years; no history of cancer; presence of dental pathology.

Exclusion criteria:

Systemic disease; malignancy; pregnancy/lactation; antibiotic use within 3 months; age <24 or >80 years.

2.3. Clinical and Radiological Assessment

All participants underwent standardized clinical and radiological examination.

Periodontal Evaluation

Periodontal pockets were assessed using a calibrated periodontal probe. The number of sites with probing depth ≥4 mm was recorded.

Examiner calibration was performed prior to the study on 10 patients. Intra-examiner reliability showed high agreement (intraclass correlation coefficient [ICC] = 0.89).

Radiological Evaluation

Orthopantomography (OPT) and cone-beam computed tomography (CBCT) were performed. Carious lesions were measured using Romexis software (v4.4.2), recording the maximum lesion diameter. Periapical lesions were assessed on both imaging modalities.

Radiological parameters:

OPT: 70–74 kV; 10–12.5 mA; 15–16 s

CBCT: 85–90 kV; 8–12.5 mA; 13.7–16 s

Radiographic interpretation was performed by an experienced radiologist blinded to biomarker data. Intra-observer reliability for lesion measurements demonstrated excellent agreement (ICC = 0.92).

2.4. Serum Biomarker Analysis

Blood Collection and Processing

Venous blood samples were collected under standardized conditions. After clotting (30–45 min), samples were centrifuged at 4500 rpm for 5 min at 15 °C. Serum was aliquoted and stored at −80 °C until analysis to prevent degradation and repeated freeze–thaw cycles.

ELISA Quantification

Serum Dickkopf-1 (Dkk-1) and tartrate-resistant acid phosphatase 5B (TRAP-5B) were quantified using commercial sandwich ELISA kits according to manufacturer protocols.

Dkk-1: detection range 31.25–2000 pg/mL; sensitivity <20 pg/mL; intra-/inter-assay CV <8%/<10%.

TRAP-5B: detection range 0.5–20 ng/mL; sensitivity <0.1 ng/mL; intra-/inter-assay CV <10%/<12%.

All samples were analyzed in duplicate. Optical density was measured at 450 nm, and concentrations were calculated from standard calibration curves. Laboratory personnel were blinded to clinical and radiological findings.

2.5. Statistical Analysis

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Statistical analysis was performed using SPSS v27.0 and Statistica v14.0.

Normality was assessed using the Shapiro–Wilk test. Continuous variables were expressed as mean ± SD or median (IQR), as appropriate. Between-group comparisons were conducted using Student's t-test or the Mann–Whitney U test. Categorical variables were analyzed using chi-square or Fisher's exact test.

Correlations between radiological findings and serum biomarkers were evaluated using Pearson's or Spearman's coefficients. Effect sizes (Cohen's d or r) were calculated to quantify the magnitude of differences.

All tests were two-tailed, with $p \leq 0.05$ considered statistically significant.

3. Results

3.1. Demographic Characteristics

The study included 63 participants (60.3% male). The control group comprised 30 individuals (15 males and 15 females), and the cancer group included 33 patients (69.7% male). No significant differences were observed between groups regarding sex distribution ($p > 0.05$).

The overall mean age was 52.67 ± 12.24 years. Mean age did not differ significantly between the control group (53.87 ± 10.76 years) and the cancer group (51.58 ± 13.52 years) ($p > 0.05$).

3.2. Clinical Characteristics of the Cancer Group

Among cancer patients, laryngeal tumors were the most frequent (72.7%), followed by sinonasal (15.2%) and oropharyngeal neoplasms (12.1%). Radiomucositis grade 3 was observed in 60.6% of cases, and grade 4 in 39.4%, as detailed in Table 1.

Patients with laryngeal tumors were younger (49.96 ± 12.97 years) compared with those diagnosed with sinonasal tumors (58.80 ± 16.24 years).

Table 1. Distribution of cancer types and radiomucositis grades in the study group (n = 33).

Cancer Type	n	%	Radiomucositis Grade	n	%
Laryngeal neoplasm	24	72.7	Grade 3	20	60.6
Oropharyngeal neoplasm	4	12.1	Grade 4	13	39.4
Sinonasal neoplasm	5	15.2	—	—	—
Total	33	100	**Total**	33	100

3.3. Periodontal Findings

The mean number of periodontal pocket sites per patient was higher in the cancer group (0.67 ± 1.32) compared with the control group (0.37 ± 0.81); however, this difference was not statistically significant ($p = 0.276$).

When analyzed by arch, no statistically significant differences were observed for maxillary ($p = 0.547$) or mandibular ($p = 0.312$) periodontal pockets between groups. Detailed descriptive statistics are presented in Table 2.

Table 2. Comparative descriptive statistics of periodontal pocket distribution between the control and cancer groups.

Variable	Group	n	Mean	SEM	SD	Min	Max	*t* value	*p* value
Total periodontal pockets	Control	30	0.37	0.15	0.81	0	3	-1.101	0.276
	Cancer	33	0.67	0.23	1.32	0	5		
	Total	63	0.52	0.14	1.11	0	5		
Maxillary periodontal pockets	Control	30	0.20	0.12	0.66	0	3	-0.605	0.547
	Cancer	33	0.30	0.12	0.68	0	2		
	Total	63	0.25	0.09	0.67	0	3		

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Mandibular periodontal pockets	Control	30	0.17	0.10	0.53	0	2	-1.019	0.312
	Cancer	33	0.36	0.16	0.93	0	4		
	Total	63	0.27	0.10	0.77	0	4		

Abbreviations: SEM—standard error of the mean; SD—standard deviation.

3.4. Dental Caries Assessment

3.4.1. Orthopantomography (OPT)

The total number of carious lesions ranged from 0 to 8 per patient. Controls exhibited a higher mean number of total caries (2.97 ± 2.48) compared with cancer patients (2.06 ± 2.29), although the difference was not statistically significant (p = 0.137).

No significant differences were observed between groups for maxillary or mandibular caries distribution.

Regarding maximum lesion depth, controls presented higher values (2.90 ± 1.56) compared with cancer patients (2.06 ± 1.92), without reaching statistical significance (p = 0.061). A significant difference was identified at the maxillary level (p = 0.027). Complete OPT data are summarized in Table 3.

Table 3. Dental caries (OPT exam)- descriptive statistics (control group, study group).

Parameter	Group	N	Mean	SEM	SD	Min	Max	Median	t (Student)	p
Total dental caries (OPT) – number	Control	30	2.97	0.454	2.484	0	8	2.00	1.506	0.137
	Study	33	2.06	0.399	2.290	0	8	1.00		
	Total	63	2.49	0.303	2.409	0	8	2.00		
Maxillary dental caries (OPT) – number	Control	30	1.37	0.251	1.377	0	4	1.00	1.422	0.160
	Study	33	0.85	0.262	1.503	0	6	0.00		
	Total	63	1.10	0.183	1.456	0	6	0.00		
Mandibular dental caries (OPT) – number	Control	30	1.60	0.341	1.868	0	6	1.00	0.909	0.367
	Study	33	1.21	0.264	1.516	0	5	1.00		
	Total	63	1.40	0.213	1.690	0	6	1.00		
Total dental caries (OPT) – maximum depth	Control	30	2.90	0.285	1.561	0	4	4.00	1.911	0.061
	Study	33	2.06	0.334	1.919	0	4	2.00		
	Total	63	2.46	0.226	1.794	0	4	4.00		
Maxillary dental caries (OPT) – maximum depth	Control	30	2.13	0.328	1.795	0	4	3.00	2.268	0.027*
	Study	33	1.15	0.286	1.642	0	4	0.00		
	Total	63	1.62	0.223	1.773	0	4	0.00		
Mandibular dental caries (OPT) – maximum depth	Control	30	2.03	0.341	1.866	0	4	2.50	0.719	0.475
	Study	33	1.70	0.321	1.845	0	4	1.00		
	Total	63	1.86	0.233	1.848	0	4	1.00		

SEM – standard error of the mean; **SD** – standard deviation.

Statistically significant at p < 0.05.

3.4.2. Cone-Beam Computed Tomography (CBCT)

CBCT analysis revealed a significantly higher mean number of total carious lesions in controls (2.97 ± 2.48) compared with cancer patients (1.85 ± 1.89) (p = 0.048).

Arch-specific comparisons (maxilla and mandible) did not demonstrate statistically significant differences (p > 0.05).

Maximum lesion depth was greater in controls (2.90 ± 1.56) than in cancer patients (2.09 ± 1.89), although this difference did not reach statistical significance (p = 0.068). Detailed CBCT findings are presented in Table 4.

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Table 4. Descriptive statistics of dental caries assessed by CBCT examination in the control and study groups.

Variable	Group	N	Mean	SEM	SD	Min	Max	Median	t (Student)	p-Value
Total dental caries (CBCT)—no.	Control	30	2.97	0.454	2.484	0	8	2.00	2.022	0.048*
	Study	33	1.85	0.329	1.889	0	6	2.00		
	Total	63	2.38	0.283	2.246	0	8	2.00		
Maxillary dental caries (CBCT)—no.	Control	30	1.37	0.251	1.377	0	4	1.00	1.935	0.058
	Study	33	0.76	0.195	1.119	0	4	0.00		
	Total	63	1.05	0.161	1.275	0	4	1.00		
Mandibular dental caries (CBCT)—no.	Control	30	1.60	0.341	1.868	0	6	1.00	1.246	0.217
	Study	33	1.09	0.236	1.355	0	5	1.00		
	Total	63	1.33	0.205	1.626	0	6	1.00		
Total dental caries (CBCT)—maximum depth	Control	30	2.90	0.285	1.561	0	4	4.00	1.857	0.068
	Study	33	2.09	0.330	1.893	0	4	2.00		
	Total	63	2.48	0.224	1.777	0	4	4.00		
Maxillary dental caries (CBCT)—maximum depth	Control	30	2.13	0.328	1.795	0	4	3.00	1.954	0.055
	Study	33	1.27	0.296	1.701	0	4	0.00		
	Total	63	1.68	0.225	1.785	0	4	1.00		
Mandibular dental caries (CBCT)—maximum depth	Control	30	2.03	0.341	1.866	0	4	2.50	0.859	0.394
	Study	33	1.64	0.313	1.800	0	4	1.00		
	Total	63	1.83	0.230	1.828	0	4	1.00		

*Statistically significant at $p < 0.05$.
Abbreviations: SEM, standard error of the mean; SD, standard deviation.

3.5. Serum Biomarker Levels

Significant intergroup differences were identified for both evaluated biomarkers (Table 5).

Table 5. Comparative descriptive statistics of ELISA kit biomarkers in the control and study groups.

Biomarker	Group	N	Mean	SEM	SD	Min	Max	t (Student)	p-Value
TRAP-5b	Control	30	0.3034	0.00263	0.01441	0.26935	0.33186	−11.405	<0.001**
	Study	30	0.3539	0.00357	0.01953	0.32018	0.39184		
	Total	60	0.3287	0.00396	0.03064	0.26935	0.39184		
Dkk-1	Control	30	1.7121	0.01833	0.10040	1.30837	1.84554	18.391	<0.001**
	Study	30	1.2100	0.02023	0.11083	0.92538	1.38710		
	Total	60	1.4610	0.03538	0.27403	0.92538	1.84554		

Values are expressed as mean ± standard error of the mean (SEM).
Statistical analysis was performed using the independent samples Student's *t*-test.
**Statistically significant at $p < 0.001$.
Abbreviations: SEM, standard error of the mean; SD, standard deviation.

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TRAP-5B levels were significantly higher in cancer patients (0.3539 ± 0.0195) compared with controls (0.3034 ± 0.0144) ($t = -11.405$, $p < 0.001$).

Conversely, Dkk-1 levels were significantly lower in cancer patients (1.2100 ± 0.1108) compared with controls (1.7121 ± 0.1004) ($t = 18.391$, $p < 0.001$).

3.6. Correlation Analysis

Correlation analysis (Table 6) demonstrated predominantly weak associations between serum biomarkers and oral parameters in both groups. In controls, TRAP-5B exhibited a statistically significant moderate positive correlation with mandibular caries ($r = 0.425$, $p < 0.05$), suggesting a potential relationship between localized carious burden and systemic osteoclastic activity. Weak inverse correlations were observed between TRAP-5B and periodontal pocket parameters. In contrast, cancer patients showed generally weak and inconsistent correlations, indicating a possible alteration of the physiological oral–systemic relationship in the oncologic setting.

Dkk-1 demonstrated weak and non-significant correlations with most evaluated oral parameters in both groups, suggesting a less direct association with localized inflammatory burden compared with TRAP-5B.

Table 6. Correlation between Serum Biomarkers and Oral Parameters in Control and Cancer Groups.

Biomarker	Oral Parameter	Control (r/ϱ; p)	Effect Size	Cancer (r/ϱ; p)	Effect Size
TRAP-5B	Total periodontal pockets	−0.302; p > 0.05	Weak	0.189; p > 0.05	Weak
	Mandibular periodontal pockets	−0.360; p > 0.05	Weak–Moderate	0.241; p > 0.05	Weak
	Total caries (OPT)	0.285; p > 0.05	Weak	−0.272; p > 0.05	Weak
	Mandibular caries (OPT)	0.425; p < 0.05	Moderate	−0.189; p > 0.05	Weak
	Total caries (CBCT)	−0.269; p > 0.05	Weak	−0.269; p > 0.05	Weak
	Maximum caries depth (CBCT)	−0.357; p > 0.05	Weak–Moderate	NS	—
	Total periapical lesions (CBCT)	0.271; p > 0.05	Weak	0.137; p > 0.05	Weak
Dkk-1	Total periodontal pockets	NS	—	0.103; p > 0.05	Weak
	Maxillary periodontal pockets	−0.248; p > 0.05	Weak	0.203; p > 0.05	Weak
	Mandibular periodontal pockets	0.193; p > 0.05	Weak	NS	—
	Total caries (OPT)	0.204; p > 0.05	Weak	NS	—
	Mandibular caries (CBCT)	NS	—	−0.150; p > 0.05	Weak
	Total periapical lesions (CBCT)	NS	—	−0.109; p > 0.05	Weak

Abbreviations

r — Pearson correlation coefficient

ϱ — Spearman correlation coefficient

NS — not statistically significant ($p > 0.05$)

Effect size interpretation:

- $|r| < 0.30$ = weak
- 0.30–0.49 = moderate
- ≥0.50 = strong

4. Discussion

The present study demonstrates a distinct systemic bone turnover profile in patients with head and neck cancer compared with healthy controls, characterized by elevated TRAP-5b and reduced Dkk-1 concentrations. These findings suggest a cancer-associated imbalance in bone remodeling, with predominant osteoclastic activation and altered Wnt/β-catenin signaling.

TRAP-5b is a specific marker of osteoclast number and resorptive activity, and its elevation in oncologic patients is consistent with enhanced osteoclastogenesis and tumor-driven bone catabolism, as previously described by Rissanen et al. [52]. Furthermore, the clinical utility of TRAP-5b as an indicator of metastatic burden has been reported by Chao et al. [53], supporting its relevance in malignancy-associated bone remodeling.

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Conversely, Dkk-1, a key inhibitor of the Wnt signaling pathway and regulator of osteoblast differentiation, was significantly reduced in cancer patients. While Dkk-1 has been implicated in tumor progression and osteolytic mechanisms in squamous cell carcinoma Ogoshi et al. [54], its regulation appears partially independent of acute inflammatory status Garnero et al. [55]. The decreased Dkk-1 levels observed in the present cohort may therefore reflect systemic tumor-related modulation of bone formation pathways rather than local oral inflammatory activity.

Importantly, the pattern of correlations between TRAP-5b and oral inflammatory parameters differed between groups. In healthy individuals, moderate associations suggest physiological coupling between local inflammatory burden and systemic bone turnover. In contrast, the predominantly weak and inverse correlations observed in oncologic patients indicate disruption of this coupling, likely mediated by tumor-derived cytokines, systemic inflammation, and metabolic alterations that override local oral influences.

Radiological findings were consistent across orthopantomography (OPT) and cone-beam computed tomography (CBCT), supporting methodological robustness. The diagnostic advantages of OPT in comprehensive jaw assessment have been described by Gil et al. [56], although reproducibility limitations were highlighted by Halse et al. [57]. CBCT provides enhanced detection of dental and periodontal lesions Tyndall and Rathore [58], reinforcing the reliability of the imaging-based correlations observed.

Collectively, these findings support a model in which malignancy induces systemic remodeling dysregulation characterized by increased osteoclast activity and altered Wnt pathway modulation. Under such conditions, oral inflammatory burden appears to exert a secondary influence on circulating biomarkers.

4.1. Clinical and Biological Implications

The dissociation between local oral pathology and systemic bone turnover markers in oncologic patients suggests that interpretation of TRAP-5b and Dkk-1 must account for systemic disease status. In cancer, these biomarkers may reflect global tumor–bone interactions rather than localized inflammatory processes.

This has potential implications for risk stratification, monitoring of skeletal involvement, and multidisciplinary management of patients undergoing oncologic therapy.

4.2. Study Limitations

This study is limited by its cross-sectional design, which precludes causal inference. The relatively small sample size may have reduced statistical power for detecting moderate associations. Biomarkers were assessed at a single time point, and longitudinal dynamics were not evaluated. Additionally, cancer stage, therapeutic exposure, and systemic inflammatory indices were not stratified. Although both OPT and CBCT were used, early subclinical lesions may remain radiographically undetected.

Future longitudinal and mechanistic studies are required to clarify the temporal relationship between tumor progression, bone turnover dysregulation, and oral inflammatory burden.

5. Conclusions

The present findings demonstrate a significant relationship between Dkk-1 and TRAP-5b, two key regulators of bone remodeling and resorption, supporting their potential utility as systemic indicators of periodontal bone metabolism. The observed biomarker profile suggests that alterations in osteoclastic activity and Wnt pathway modulation may contribute to periodontal bone dynamics and provide a biological rationale for the consideration of regenerative therapeutic strategies in periodontal disease management.

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Furthermore, given the systemic remodeling imbalance identified in patients with head and neck cancer, comprehensive oral evaluation and rehabilitation should be performed prior to radiotherapy to reduce treatment-related complications and optimize oncologic outcomes.

Author Contributions: Conceptualization, C.A. and M.S.; methodology, A.C.C. and S.S.; formal analysis, E.R.C. and R.M.P.; resources, C.A. and E.R.C.; data curation, A.C.C., M.S. and E.R.C.; writing—original draft preparation, C.A. and E.R.C.; writing—review and editing, S.S., and M.S..; visualization, A.C.C., and E.R.C.; supervision, M.S. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki. Ethical approval for the conduct of this study was obtained from the Ethics Committee of Grigore T. Popa University of Medicine and Pharmacy in Iasi (Approval No. 85/26.05.2021).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient(s) to publish this paper.

Data Availability Statement: All the data used in this study are available on request from the corresponding author.

Conflicts of Interest: The authors declare no conflicts of interest.

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