BRITISH JOURNAL OF HOSPITAL MEDICINE

ARTICLE

Clinical Significance of Aging-Related Secretory Phenotypic Factors in Diagnosing Type 2 Diabetes Mellitus-Associated Peri-Implantitis: A Retrospective Analysis

Wei Chen[1], Siyi Chen[2,*], Jiqin Zhang[3,*]

[1]Department of Stomatology, Linping Campus, The Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, Zhejiang, China
[2]Department of Stomatology, Yunhe County People's Hospital, Lishui, Zhejiang, China
[3]Department of Stomatology, The Third Affiliated Hospital Zhejiang Chinese Medical University (Zhejiang Zhongshan Hospital), Hangzhou, Zhejiang, China
*Correspondence: yhcsy1990@163.com (Siyi Chen); 18268856053@163.com (Jiqin Zhang)

Abstract

Aims/Background Type 2 diabetes mellitus (T2DM) has been reported as a critical contributor to peri-implantitis. Hyperglycemia and associated metabolic changes in diabetes promote cellular senescence. This study aims to investigate the significance of aging-related secretory factors, known as senescence-associated secretory phenotypes (SASPs), in peri-implant crevicular fluid (PICF) in diagnosing type 2 diabetes mellitus-associated peri-implantitis (T2DM-PI).

Methods This study included 72 patients with T2DM-PI (designated as a T2DM-PI group) and 45 patients with peri-implantitis (as a control group). The patients were selected at the Linping Campus of the Second Affiliated Hospital of Zhejiang University School of Medicine between December 2021 and December 2023. Patients in both groups were further divided into the middle-aged group and the elderly group. Furthermore, patients were stratified as the middle-aged peri-implantitis (M-PI) group, the middle-aged type 2 diabetes mellitus-associated peri-implantitis (M-DPI) group, the elderly peri-implantitis (E-PI) group, and the elderly type 2 diabetes mellitus-associated peri-implantitis (E-DPI) group. Baseline characteristics and the level of SASPs in PICF were compared between the two groups. We analyzed the factors influencing the occurrence of peri-implantitis in type 2 diabetes, conducted multiple collinearity testing on the selected variables, and incorporated variables with a variance inflation factor (VIF) <5 into a multi-factor binary logistic regression analysis to identify independent risk factors for type 2 diabetes mellitus-associated peri-implantitis. Furthermore, a receiver operating characteristic (ROC) curve was constructed to assess the diagnostic value of SASP levels in patients with T2DM-PI.

Results Compared to the control group, the level of SASPs was significantly higher in the T2DM-PI group, with elevated SASP levels positively correlated with the severity of periodontal indicators. Binary logistic regression analysis identified body mass index (BMI), interleukin (IL)-1β, tumor necrosis factor (TNF)-α, and matrix metalloproteinase 8 (MMP8) as independent risk factors for the occurrence of T2DM-PI in the middle-aged group ($p < 0.05$). BMI was found to be an independent risk factor for T2DM-PI in the elderly group ($p < 0.05$). The ROC curve analysis revealed that IL-1β had the highest diagnostic accuracy among the middle-aged T2DM-PI, with an area under the curve (AUC) of 0.861, a sensitivity of 85.40%, and a specificity of 82.10%. BMI demonstrated the highest diagnostic accuracy in elderly T2DM-PI, with an AUC of 0.904, a sensitivity of 100%, and a specificity of 70.60%.

Conclusion Elevated SASP levels in PICF are associated with the severity of periodontal index outcomes in patients with T2DM-PI. Furthermore, SASP levels hold significant diagnostic performance for T2DM-PI.

Key words: senescence-associated secretory phenotype; periodontal index; peri-implantitis; type 2 diabetes

Submitted: 28 March 2025 Revised: 8 July 2025 Accepted: 24 July 2025

How to cite this article:
Chen W, Chen S, Zhang J. Clinical Significance of Aging-Related Secretory Phenotypic Factors in Diagnosing Type 2 Diabetes Mellitus-Associated Peri-Implantitis: A Retrospective Analysis. Br J Hosp Med. 2025. https://doi.org/10.12968/hmed.2025.0294

Introduction

Since the beginning of the 21st century, implant fixed dentures have gradually become one of the most preferred clinical options for clinical restoration of missing teeth due to their advantages, such as the preservation of adjacent teeth, good comfort, excellent occlusion recovery, improved aesthetics, and long intraoral retention. However, complications such as inflammation of peri-implant connective tissue and progressive loss of supporting bone can lead to peri-implantitis (Monje et al, 2024). Even after treatment, peri-implantitis may lead to irreversible damage to peri-implant tissues, impacting the stability of the implanted teeth (Carcuac et al, 2020). Peri-implantitis is affected by several risk factors, including a history of periodontitis, inadequate oral hygiene, and unhealthy living habits such as smoking (Darby, 2022). Diabetes mellitus is another crucial risk factor for peri-implantitis. It is a common metabolic disorder primarily caused by persistent hyperglycemia due to insulin resistance, insufficient insulin secretion, or excessive glucagon secretion. Type 2 diabetes mellitus (T2DM), which accounts for about 90–95% of diabetic cases, has been reported as a critical contributor to peri-implantitis. The severity of peri-implantitis in T2DM cases increases proportionally with inadequate glycemia control (Ali et al, 2022; Nibali et al, 2022).

Furthermore, hyperglycemia and associated metabolic changes in diabetes promote cellular senescence. The senescence-associated secretory phenotype (SASP), a marker of cellular aging, consists of various secretory factors, such as pro-inflammatory cytokines, chemokines, growth factors, and matrix-degrading enzymes, that exert autocrine and paracrine effects (Ok et al, 2021). For example, evidence indicates that elderly patients with chronic apical inflammatory lesions exhibit higher levels of inflammatory cytokines, including interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α, as compared to adult controls (Teixeira et al, 2021). Similarly, matrix metalloproteinases (MMPs), which are critical mediators of collagen degradation, were found to be upregulated in the periodontal tissues of elderly individuals (Kageyama et al, 2022; Rattanaprukskul et al, 2025). Additionally, advanced glycation end products (AGEs), another key aging biomarker, bind to their receptor for advanced glycation end products (RAGE), further promoting tissue aging (Kageyama et al, 2022; Rattanaprukskul et al, 2025). Furthermore, Yang et al (2023) reported that the number of senescent cells elevated over time in the subepithelial connective tissue and alveolar bone surrounding implants. Notably, using senolytic drugs "senolytics" has demonstrated potential in reducing implant loss by inhibiting senescence-related mechanisms. However, no study to date has explored the role of senescence-associated secretory phenotypes in T2DM-related peri-implantitis.

Traditionally, implant health is primarily assessed by measuring the periodontal pocket depth employing a periodontal probe and observing bleeding upon probing. However, this strategy has limitations due to the lack of periodontal ligaments around the implant and the impact of prosthetic designs. Additionally, implant mucosal seals are usually less resistant to probing compared to natural teeth, which may lead to false-positive mechanical bleeding even in healthy implants (Alassy

et al, 2019). Therefore, identifying additional diagnostic markers is crucial for improving early detection of both periodontitis and peri-implantitis.

However, current investigations into peri-implantitis in patients with type 2 diabetes largely focus on risk factors, with a lack of objective and specific assessment tools. Peri-implant crevicular fluid (PICF) is a promising source of biomarkers for diagnosing and predicting peri-implant disease. Studies have shown that assessing biomarker levels in gingival fluid is effective for determining the severity of periodontitis around implants in T2DM patients (Dŏgan et al, 2015; Delucchi et al, 2023). A recent study reported that endothelin-1 levels in PICF were significantly increased in peri-implant mucositis, allowing for earlier and more accurate detection of peri-implantitis (Saito et al, 2024). Investigating the host-derived biomarkers in gingival crevicular fluid (GCF) or PICF offers valuable insights for early diagnosis, prognosis, and potential treatment planning for chronic inflammatory conditions.

Therefore, this study aims to analyze the level of aging-related secretory phenotypic factors in the PICF of patients with type 2 diabetes mellitus-associated peri-implantitis (T2DM-PI) and explore its diagnostic value in assessing peri-implantitis. The findings would enable earlier intervention and improve clinical outcomes among T2DM-PI.

Methods

Selection of Study Participants and Collection of Clinical Data

This study selected peri-implantitis patients diagnosed at the Linping Campus of the Second Affiliated Hospital of Zhejiang University School of Medicine between December 2021 and December 2023. T2DM was diagnosed according to the diagnostic criteria established by the World Health Organization (WHO) and the American Diabetes Association (ADA) (Puavilai et al, 1999; Li et al, 2020a). Peri-implantitis was defined based on a probing depth (PD) $\geq$6 mm and a crestal bone loss (CBL) $\geq$3 mm, following the Armitage Criteria of Periodontology (Armitage, 1999). The study was approved by the Ethics Committee of the Second Affiliated Hospital of Zhejiang University School of Medicine (No. 2021-053), and all procedures complied with the Declaration of Helsinki.

Applying the sample size calculation formula ($N = 2 \times \left[\frac{Z_{\alpha/2}+Z_{\beta}}{\Delta/\sigma}\right]^2$), the required sample size was calculated. Assuming an estimated effect size of 0.6 mm increase in pocket depth, with $\alpha = 0.05$, power = 0.8, and the effect standard deviation of 0.75 mm, the minimum sample size was determined to be 25 patients. Based on patient records from December 2021 to December 2023, a total of 72 patients with T2DM-PI and 45 patients with conventional peri-implantitis were finally included.

Given the age-related characteristics of periodontitis and T2DM, patients were further stratified into the middle-aged (35–60 years) and elderly ($\geq$61 years) groups. Ultimately, four study groups were established: the middle-aged peri-implantitis (M-PI) group, the middle-aged type 2 diabetes mellitus-associated peri-implantitis

(M-DPI) group, the elderly peri-implantitis (E-PI) group, and the elderly type 2 diabetes mellitus-associated peri-implantitis (E-DPI) group.

The inclusion criteria for patient selection were as follows: (1) presence of at least one implant diagnosed with peri-implantitis; (2) medically diagnosed T2DM patients with glycosylated hemoglobin (HbA1C) $\geq$6.5%, who had not used anti-osteoporosis or anti-inflammatory drugs within the past 6 months; (3) patient aged 35 years or above; (4) patients in the T2DM-PI groups had a confirmed diagnosis of T2DM for more than 1 years before the study, with stable glycemic control (fasting blood glucose (FBG) between 6.10–11.0 mmol/L). The exclusion criteria included (1) presence of other serious systemic diseases (such as immunosuppressive diseases, cancer, cardiovascular, hepatic, or renal diseases) in addition to T2DM; (2) pregnancy or breastfeeding; (3) history of smoking, alcohol abuse, and drug abuse; (4) use of antibiotic drugs within the past six months, and (5) unwilling to participate.

Demographic data and clinical periodontal parameters were collected, and diabetic and non-diabetic patients were compared for all parameters except PD and clinical attachment level (CAL) to reduce the effects of confounding factors. Thus, the patients were distributed as follows: M-PI group (28 patients), M-DPI group (41 patients), E-PI group (17 patients), E-DPI group (31 patients).

Outcome Measures

The outcome measures included in this study were as follows:

• Clinical data collection: Two sets of clinical data were collected, including age, gender, body mass index (BMI), cause of tooth loss, implant exercise time, probing depth (PD), CAL, gingival index (GI), plaque index (PLI), and fasting blood glucose levels.

• Sample collection: Gingival crevicular fluid (GCF) samples were collected from all patients on the day of admission. Sampling was conducted on the buccal (lip) side of each implant, with 2 proximal and distal sites selected per implant. Supragingival plaque and calculus were carefully removed, and the area was isolated using a sterile dry cotton roll to prevent contamination. The tooth surface was dried with an air syringe for 10 seconds. Sterile paper tips were gently inserted into the gingival sulcus of the implant until slight resistance was encountered, left the tips for 30 seconds, and then removed. After that, a paper strip (2 mm) was placed into a centrifuge tube containing 200 μL of phosphate-buffered saline (PBS). The samples were shaken for 30 minutes and centrifuged at 10,000 rpm for 10 minutes (radius: 10 cm) at 4 °C. The resultant supernatant was collected for subsequent analysis.

• Cytokine analysis: The concentrations of senescence-associated secretory phenotype (SASP)-related cytokines, including interleukin (IL)-1β (PI305, Beyotime, Shanghai, China), IL-6 (PI330, Beyotime, Shanghai, China), tumor necrosis factor (TNF)-α (PT518, Beyotime, Shanghai, China), intercellular adhesion molecule (ICAM)-1 (PI498, Beyotime, Shanghai, China), C-C motif chemokine ligand-2 (CCL2) (PC130, Beyotime, Shanghai, China), matrix metalloproteinase 1 (MMP1) (ab215083, Abcam, Cambridge, UK), MMP8 (ab219050, Abcam, Cam-

Table 1. Comparison of baseline characteristics between the M-PI and M-DPI groups.

Variable	M-PI (n = 28)	M-DPI (n = 41)	$t/Z/\chi^2$	*p*-value
Gender			0.777	0.378
Male (n, %)	16 (57.14)	19 (46.34)		
Female (n, %)	12 (42.86)	22 (53.66)		
Age [M (Q1, Q3)]	49.00 (45, 56)	49.00 (46, 56)	0.141	0.888
BMI [kg/cm^2, $\bar{x} \pm s$]	23.68 ± 1.96	25.83 ± 3.39	3.024	0.004
Fasting blood glucose [mmol/L, M (Q1, Q3)]	5.40 (5.10, 5.60)	8.40 (7.70, 9.60)	7.019	<0.001
Cause of tooth loss			5.104	0.084
Periodontal disease (n, %)	8 (28.57)	20 (48.78)		
Teeth defect (n, %)	13 (46.43)	18 (43.90)		
Trauma (n, %)	7 (25.00)	3 (7.32)		
Mean PD [mm, M (Q1, Q3)]	3.58 (3.37, 3.68)	4.57 (4.35, 4.69)	6.991	<0.001
Mean CAL [mm, $\bar{x} \pm s$]	3.73 ± 0.35	4.18 ± 0.31	5.618	<0.001
GI				0.923
0 (n, %)	0 (0.00)	0 (0.00)		
1 (n, %)	2 (7.14)	3 (7.32)		
2 (n, %)	7 (25.00)	12 (29.27)		
3 (n, %)	19 (67.86)	26 (63.41)		
PLI				0.928
0 (n, %)	0 (0.00)	0 (0.00)		
1 (n, %)	2 (7.14)	3 (7.32)		
2 (n, %)	12 (42.86)	20 (48.78)		
3 (n, %)	14 (50.00)	18 (43.90)		

M-PI, middle-aged peri-implantitis; M-DPI, middle-aged type 2 diabetes mellitus-associated peri-implantitis; BMI, body mass index; PD, probing depth; CAL, clinical attachment level; GI, gingival index; PLI, plaque index; M, Median.

bridge, UK), receptor-activator of nuclear factor-κB ligand (RANKL) (MM-1513H, Jiangsu Mei-mian Industrial Co., Ltd., Yancheng, China) and receptor for advanced glycation end products (RAGE) (EK1103, Lianke Biotechnology Co., Ltd., Hangzhou, China), were quantified using standard enzyme-linked immunosorbent assay (ELISA) kits. All SASP-related factor assessments were conducted in triplicate, and the results of each set of three were averaged. Final concentration is expressed in pg/mL.

Statistical Analysis

Data were statistically analyzed using SPSS 27.0 software (IBM Corp., Armonk, NY, USA). Measurement data following a normal distribution, as determined by the Kolmogorov-Smirnov test, were expressed as mean ± standard deviation ($\bar{x} \pm s$), and comparisons between two groups were conducted using the independent-samples *t*-test. However, non-normally distributed measurement data were expressed as Median (Q1, Q3), with intergroup comparisons performed using the Mann-Whitney U test.

Categorical variables (counting data) were expressed as frequency and percentage (%), and between-group comparisons were performed using the χ^2 test

Table 2. Comparison of baseline characteristics between the E-PI and E-DPI groups.

Variable	E-PI (n = 17)	E-DPI (n = 31)	$t/Z/\chi^2$	p-value
Sex			0.016	0.900
Male (n, %)	9 (52.94)	17 (54.84)		
Female (n, %)	8 (47.06)	14 (45.16)		
Age [M (Q1, Q3)]	64 (62, 64)	66 (63,67)	1.015	0.316
BMI [kg/cm^2, $\bar{x} \pm s$]	23.12 ± 1.96	26.58 ± 1.71	6.369	<0.001
Fasting blood glucose [mmol/L, $\bar{x} \pm s$]	5.28 ± 0.42	8.58 ± 1.00	12.945	<0.001
Cause of tooth loss			0.279	1.000
Periodontal disease (n, %)	10 (58.82)	18 (58.06)		
Teeth defect (n, %)	6 (35.29)	10 (32.26)		
Trauma (n, %)	1 (5.88)	3 (9.68)		
Mean PD [mm, $\bar{x} \pm s$]	3.48 ± 0.27	4.40 ± 1.39	2.689	0.005
Mean CAL [mm, $\bar{x} \pm s$]	3.71 ± 0.39	4.62 ± 0.36	8.134	<0.001
GI				0.703
0 (n, %)	0 (0.00)	0 (0.00)		
1 (n, %)	0 (0.00)	1 (3.23)		
2 (n, %)	5 (29.41)	12 (38.71)		
3 (n, %)	12 (70.59)	18 (58.06)		
PLI				0.300
0 (n, %)	0 (0.00)	0 (0.00)		
1 (n, %)	3 (17.65)	3 (9.68)		
2 (n, %)	2 (11.76)	10 (32.26)		
3 (n, %)	12 (70.59)	18 (58.06)		

E-PI, elderly peri-implantitis; E-DPI, elderly type 2 diabetes mellitus-associated peri-implantitis.

or Fisher's exact test where appropriate. Correlation analysis was performed using Pearson's linear correlation or Spearman's rank correlation analysis, based on the data distribution.

Collinearity analysis was performed on statistically significant indicators identified in univariate analysis to address potential multicollinearity issues. Logistic regression analysis was used to identify risk factors associated with T2DM-PI. The diagnostic performance of relevant indicators was assessed using receiver operating characteristic (ROC) curve analysis. A p-value < 0.05 was set as a statistically significant threshold.

Results

Comparison of Basic Clinical and Demographic Characteristics Between the Two Groups

Tables 1,2 show the demographic characteristics, fasting blood glucose levels, and clinical periodontal parameters for the middle-aged and elderly groups, respectively. Within the same age group, compared to the PI group, the DPI group demonstrated significantly higher fasting blood glucose levels, BMI, and average

Table 3. Comparison of aging-related secretory factors in gingival crevicular fluid of four groups of patients ($\bar{x} \pm s$, M (Q1, Q3)).

Variable	M-PI (n = 28)	M-DPI (n = 41)	t/Z	p-value	E-PI (n = 17)	E-DPI (n = 31)	t/Z	p-value
IL-1β	2.05 (1.25, 2.85)	3.81 ± 1.24	5.065	<0.001	2.36 (1.45, 2.36)	3.83 ± 1.14	3.654	<0.001
IL-6	3.88 ± 1.59	4.08 ± 1.61	0.513	0.610	3.47 ± 1.34	3.95 ± 1.14	1.311	0.196
TNF-α	5.56 ± 1.94	7.41 ± 1.63	4.288	<0.001	6.47 ± 1.89	7.38 ± 1.81	1.633	0.109
MMP1	1.51 ± 0.62	1.88 ± 0.77	2.152	0.035	1.69 ± 0.69	1.69 ± 0.76	0.007	0.995
MMP8	1.23 ± 0.47	2.08 ± 0.82	4.965	<0.001	1.33 ± 0.61	1.87 ± 0.59	2.992	0.004
CCL2	3.57 (1.92, 4.90)	3.79 (3.22, 4.34)	1.815	0.070	2.8 (2.13, 3.92)	3.87 (3.48, 4.95)	2.113	0.035
ICAM-1	3.38 (2.40, 4.86)	3.79 ± 1.29	0.892	0.372	3.37 (1.02, 3.95)	3.72 ± 1.23	1.876	0.061
RANKL	1.64 ± 0.81	2.09 ± 1.08	1.856	0.068	1.84 ± 0.64	1.95 ± 0.93	0.425	0.673
RAGE	1.47 (0.95, 2.40)	2.23 ± 0.93	2.468	0.014	1.29 (0.94, 1.93)	2.50 ± 0.78	4.010	<0.001

IL-1β, interleukin-1β; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; MMP1, matrix metalloproteinase 1; MMP8, matrix metalloproteinase 8; CCL2, C-C motif chemokine ligand-2; ICAM-1, intercellular adhesion molecule-1; RANKL, receptor-activator of nuclear factor-κB ligand; RAGE, receptor for advanced glycation end products.

Table 4. Comparison of aging-related secretory factors in gingival crevicular fluid of two groups of patients ($\bar{x} \pm s$, M (Q1, Q3)).

Variable	M-DPI (n = 41)	E-DPI (n = 31)	t/Z	p-value
IL-1β	3.81 ± 1.24	3.83 ± 1.14	0.067	0.946
IL-6	4.08 ± 1.61	3.95 ± 1.14	0.388	0.700
TNF-α	7.41 ± 1.63	7.38 ± 1.81	0.095	0.924
MMP1	1.88 ± 0.77	1.69 ± 0.76	1.061	0.292
MMP8	2.08 ± 0.82	1.87 ± 0.59	1.221	0.226
CCL2	3.79 (3.22, 4.34)	3.87 (3.48, 4.95)	0.586	0.558
ICAM-1	3.79 ± 1.29	3.72 ± 1.23	0.242	0.810
RANKL	2.09 ± 1.08	1.95 ± 0.93	0.552	0.583
RAGE	2.23 ± 0.93	2.50 ± 0.78	1.303	0.197

values of PD and CAL ($p < 0.05$). However, there were no statistically significant differences between the PI and DPI groups in terms of gender, age, cause of tooth loss, gingival index, and plaque index across different age groups ($p > 0.05$).

Analysis of Aging-Related Secretory Factor Levels in PICF

As detailed in Table 3, the levels of several SASP-related factors in the gingival crevicular fluid were significantly increased in the M-DPI group compared to the M-PI group, including IL-1β, TNF-α, MMP1, MMP8, and RAGE ($p < 0.05$). Moreover, when comparing the E-DPI and E-PI groups, statistically significant differences were found in the levels of IL-1β, CCL2, MMP8, and RAGE ($p < 0.05$). However, no statistically significant differences were observed in SASP factor levels between the E-DPI and M-DPI groups (Table 4, $p > 0.05$).

Table 5. Correlation analysis of the indicators with significant differences in the middle-aged group.

Variable	Collinearity analysis	
	Tolerance	VIF
BMI	0.849	1.178
Fasting blood glucose	0.331	3.021
Mean PD	0.383	2.609
Mean CAL	0.567	1.765
IL-1β	0.663	1.507
TNF-α	0.755	1.325
MMP1	0.868	1.152
MMP8	0.751	1.331
RAGE	0.786	1.272

VIF, variance inflation factor.

Table 6. Correlation analysis of the indicators with significant differences in the elderly group.

Variable	Collinearity analysis	
	Tolerance	VIF
BMI	0.490	2.042
Fasting blood glucose	0.202	4.961
Mean PD	0.324	3.084
Mean CAL	0.663	1.508
IL-1β	0.663	1.509
MMP8	0.686	1.457
CCL2	0.805	1.243
RAGE	0.601	1.665

Multivariate Logistic Regression Analysis

Initially, univariate analysis was conducted on the indicators that showed significant differences, which were then included in multivariate analysis after performing multicollinearity testing. Indicators with a variance inflation factor (VIF) <5 were used as the independent variables, while the presence of T2DM-PI was included as the dependent variable (Tables 5,6). Multivariate logistic regression analysis identified BMI, IL-1β, TNF-α and MMP8 as independent risk factors for peri-implantitis ($p < 0.05$, Table 7). Moreover, BMI was found to be an independent risk factor for peri-implantitis in elderly patients with T2DM ($p < 0.05$, Table 8).

Correlation Between Aging-Related Secretory Factors and Periodontal Indicators in PICF in T2DM-PI

After observing elevated SASP levels in gingival crevicular fluid in patients with T2DM-PI, we further evaluated the association between SASP levels and the clinical parameters PD and CAL. As detailed in Table 9, Pearson correlation anal-

Table 7. Multivariate binary logistic regression analysis of T2DM-associated peri-implantitis in the middle-aged group.

Variable	β	SE	Wald	OR	95% CI	p-value
BMI	0.323	0.131	6.061	1.381	1.068–1.786	0.014
IL-1β	1.336	0.493	7.350	3.804	1.448–9.994	0.007
TNF-α	0.952	0.369	6.672	2.591	1.258–5.335	0.010
MMP1	0.302	0.930	0.105	1.352	0.218–8.376	0.746
MMP8	1.925	0.909	4.845	6.855	1.154–40.717	0.034
RAGE	0.025	0.741	0.001	1.025	0.240–4.379	0.973

CI, confidence interval; OR, odds ratio; SE, standard error; T2DM, type 2 diabetes mellitus.

Table 8. Multivariate binary logistic regression analysis of T2DM-associated peri-implantitis in the elderly group.

Variable	β	SE	Wald	OR	95% CI	p-value
BMI	1.373	0.571	5.786	3.946	1.290–12.077	0.016
IL-1β	0.705	0.736	0.916	2.024	0.478–8.571	0.338
MMP8	0.955	0.804	1.411	2.599	0.537–12.564	0.235
CCL2	0.484	0.571	0.718	1.622	0.530–4.969	0.397
RAGE	2.290	1.314	3.036	9.872	0.751–129.724	0.081

ysis (TNF-α, MMP1, MMP8 and RANKL) and Spearman correlation analysis (IL-1β, CCL2, ICAM-1, and RAGE) revealed significant associations. In the M-DPI group, the levels of IL-1β, TNF-α and MMP8 in PICF were statistically correlated with PD ($p < 0.05$), while the levels of IL-1β, MMP8, and RAGE were statistically correlated with CAL ($p < 0.05$). No significant association was found between SASP levels and CAL in other parameters ($p > 0.05$, Table 9). In the E-DPI group, the levels of MMP8 were statistically correlated with PD ($p < 0.05$, Table 9).

Clinical Significance of Aging-Related Secretory Factors in Gingival Crevicular Fluid in Diagnosing T2DM-PI

The sensitivity, specificity, and area under the ROC curve for BMI, IL-1β, TNF-α, and MMP8 in middle-aged patients with T2DM-PI are shown in Table 10 and Fig. 1. The highest diagnostic efficacy was observed at the following cutoff values: IL-1β 2.950 pg/mL, TNF-α 5.635 pg/mL, and MMP8 1.795 pg/mL. IL-1β demonstrated an area under the curve (AUC) of 0.861, with a sensitivity of 85.40% and a specificity of 82.10%. TNF-α had an AUC of 0.773, with a sensitivity of 90.20% and a specificity of 53.60%. MMP8 showed an AUC of 0.834, with a sensitivity of 73.20% and a specificity of 85.70%. BMI exhibited diagnostic accuracy at an AUC of 0.795, with a sensitivity of 61.40% and a specificity of 78.60%.

In elderly patients with T2DM-PI, BMI exhibited the highest diagnostic accuracy with an AUC of 0.904, a sensitivity of 100% and a specificity of 70.60% (Table 11 and Fig. 2).

Table 9. Correlation between aging-related secretory factors and periodontal indicators in PICF in T2DM-PI.

Variable	M-DPI				E-DPI			
	PD		CAL		PD		CAL	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*
IL-1β	0.418	<0.001	0.448	<0.001	0.006	0.959	–0.087	0.468
IL-6	0.065	0.595	0.024	0.842	0.200	0.173	0.142	0.337
TNF-α	0.356	0.003	0.177	0.145	0.163	0.267	0.159	0.280
MMP1	0.093	0.447	0.1363	0.180	0.081	0.586	0.050	0.737
MMP8	0.452	<0.001	0.310	0.010	0.301	0.038	0.027	0.856
CCL2	0.173	0.155	0.167	0.169	0.187	0.116	0.097	0.416
ICAM-1	0.136	0.264	0.048	0.698	–0.002	0.987	–0.033	0.781
RANKL	0.067	0.587	0.163	0.181	0.013	0.929	0.002	0.987
RAGE	0.150	0.220	0.283	0.018	–0.100	0.403	0.100	0.402

PICF, peri-implant crevicular fluid; T2DM-PI, type 2 diabetes mellitus-associated peri-implantitis.

Table 10. Diagnostic performance of SASPs in middle-aged patients with T2DM-associated peri-implantitis.

Factor	Cutoff	AUC	95% CI	Sensitivity (%)	Specificity (%)	*p*-value
BMI	25.500	0.795	0.692–0.899	61.40	78.60	<0.001
IL-1β	2.950	0.861	0.770–0.952	85.40	82.10	<0.001
TNF-α	5.635	0.773	0.658–0.888	90.20	53.60	<0.001
MMP8	1.795	0.834	0.735–0.932	73.20	85.70	<0.001

AUC, area under the curve; SASPs, senescence-associated secretory phenotypes.

Discussion

Peri-implantitis is an inflammatory condition that affects the osseointegration of peri-implant tissues. It often leads to complications such as periodontal pocket formation, progressive loss of supporting bone, and suppuration, thereby reducing implant survival (Afrasiabi et al, 2023). The occurrence of peri-implantitis among patients undergoing implant restoration is estimated to range from 15% to 30% (Chai et al, 2024). Although peri-implantitis is a multifactorial disease, patients with underlying conditions such as obesity or diabetes show a higher susceptibility. Particularly, compared to healthy individuals, those with diabetes have a substantially higher likelihood of developing peri-implantitis.

In this study, we detected more severe periodontal indicators in T2DM-PI patients compared to the control group, which is consistent with previous findings (Ali et al, 2022). Furthermore, we confirmed that increased SASP levels in the gingival crevicular fluid of T2DM-PI patients are positively correlated with the degree of periodontal destruction. This significant increase in aging markers within the peri-implant gingival crevicular fluid provides direct evidence for the correlation between cellular senescence, diabetes-related complications, and peri-implantitis.

Table 11. Diagnostic performance of SASPs in elderly patients with T2DM-associated peri-implantitis.

Factor	Cutoff	AUC	95% CI	Sensitivity (%)	Specificity (%)	*p*-value
BMI	23.500	0.904	0.805–0.998	100	70.60	<0.001

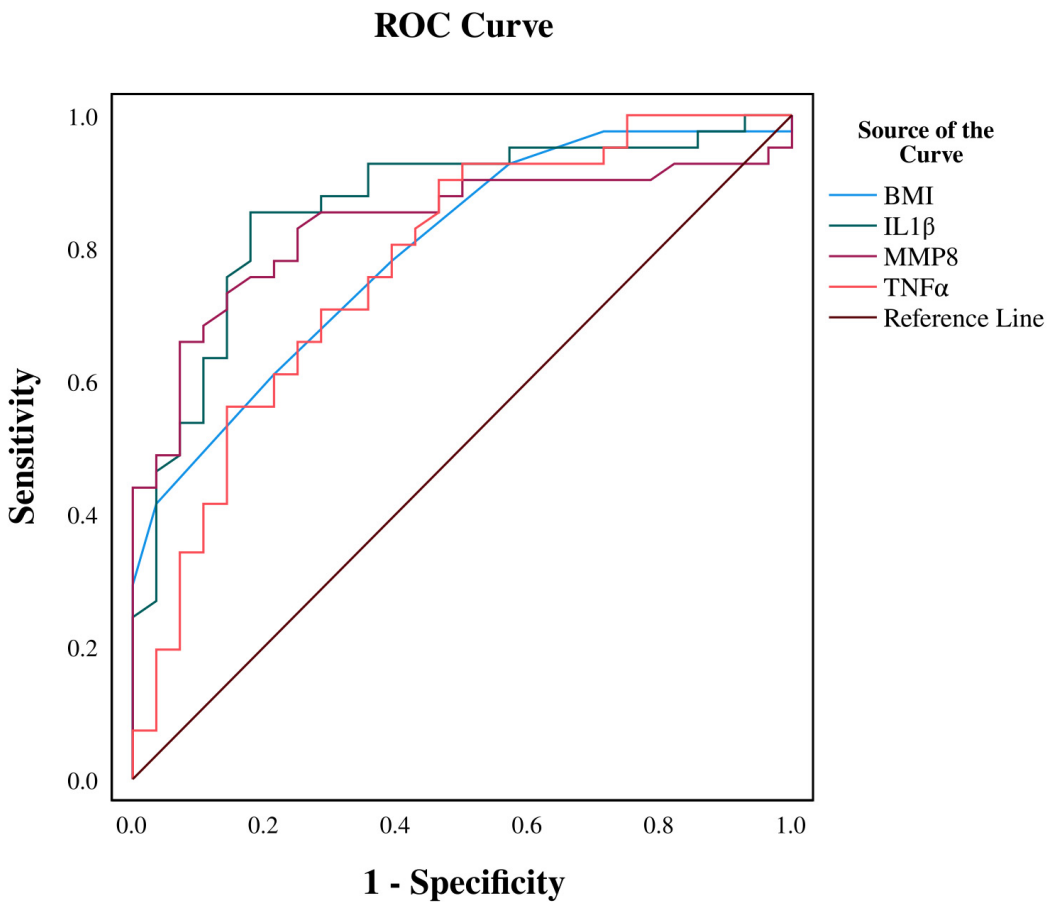

Fig. 1. ROC curves of BMI, IL-1β, TNF-α, and MMP8 for diagnosing T2DM-PI in the middle-aged group. ROC, receiver operating characteristic.

Additionally, we found an excessive inflammatory response in patients with T2DM-PI. This may be due to the hyperglycemic environment, where inflammatory SASP factors (IL-1β, TNF-α, and IL-6) induce local inflammatory responses, while CCL2 and ICAM-1 recruit immune cells such as neutrophils and macrophages, amplifying the inflammatory cascade (Song et al, 2023; Yuan et al, 2024). Furthermore, the upregulation of IL-1β secretion can, in turn, stimulate SASP production (De Cecco et al, 2019), whereas the inhibition of IL-1β reduces tissue decomposition and inflammatory progression.

Hyperglycemia and excessive inflammation can lead to unbalanced expression of matrix metalloproteinases and dysregulation of bone metabolic homeostasis (Dubois et al, 2008; Zeidán-Chuliá et al, 2018). In this study, the levels of MMP1, MMP8, and RAGE were significantly increased in T2DM-PI patients compared to PI patients, consistent with findings from multiple published studies (Figueiredo

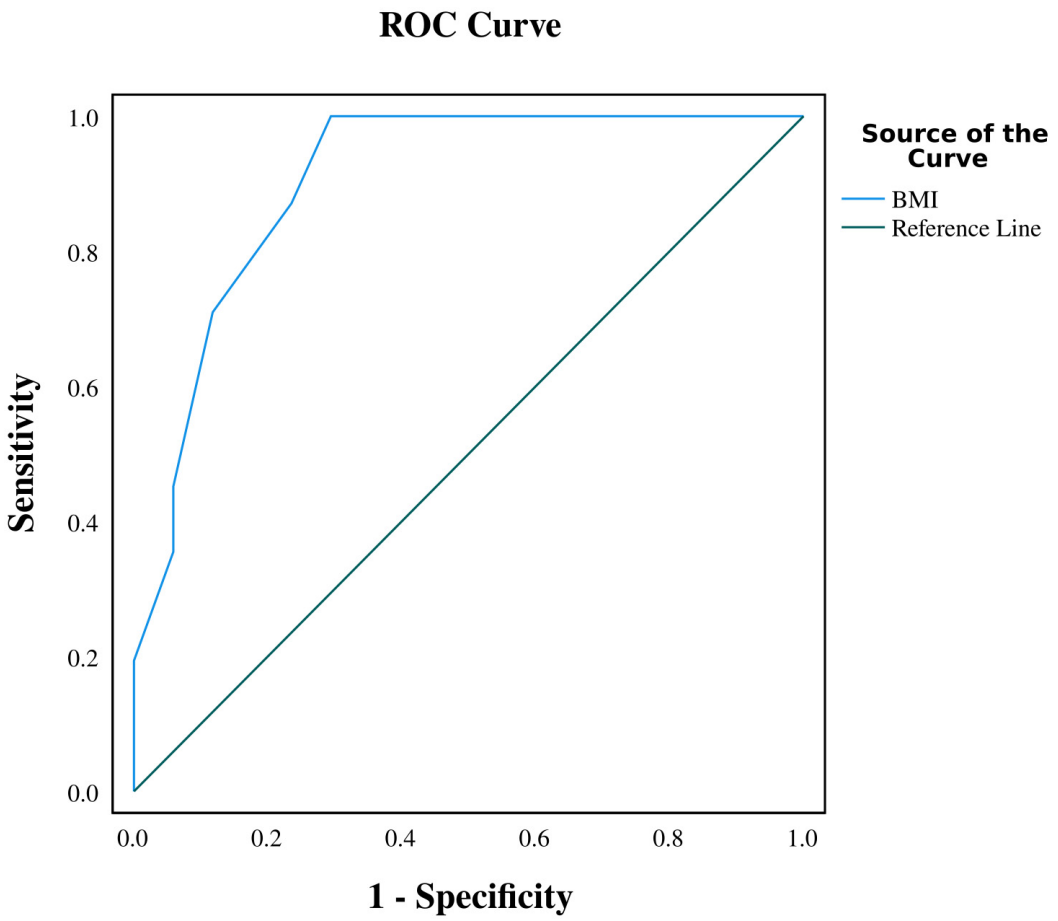

Fig. 2. ROC curve analysis of BMI for diagnosing T2DM-PI in the elderly group.

et al, 2020; Milinkovic et al, 2021; Jansson et al, 2025). Previous studies have reported that hyperglycemia in patients with T2DM enhances the accumulation of advanced glycation end products (AGEs), which bind to RAGE and induce the upregulation of destructive inflammatory cytokines, such as IL-6, IL-1β, and TNF-α, in the PICF, thereby accelerating tissue aging (Al-Aali et al, 2020; Chen and Hong, 2023; Li et al, 2024). Interestingly, our study found no statistically significant difference in RAGE levels in PICF between the elderly T2DM-PI and middle-aged T2DM-PI groups, which was inconsistent with the findings of Rajeev et al (2011). This difference may be due to the relatively small number of cases included in the study, as well as large confidence intervals and standard errors, which limit the generalizability and practical applicability of our findings.

Studies have revealed that, in addition to the increased formation of AGEs and elevated expression of SASP factors, immune dysfunction and microbial flora imbalance can contribute to increased susceptibility of diabetes mellitus (DM) patients to periodontal and peri-implant diseases. The persistent presence and hyperactivation of neutrophils in periodontal tissues can promote a chronic inflammatory state, leading to tissue damage (Cortés-Vieyra et al, 2016). Furthermore, it has been speculated that the formation of neutrophil extracellular traps (NETs) may accelerate periodontal destruction in T2DM patients. SASP components can activate neutrophils and promote NET release, while NET-derived components, such as histones, can

induce inflammatory responses in surrounding cells and stimulate additional SASP production. Excessive NET production has been observed to activate the immune response and increase periodontal tissue damage (Rajendran and Uppoor, 2018; Liang et al, 2020). Moreover, neutrophils in DM patients usually exhibit impaired chemotaxis and reduced phagocytosis, thereby decreasing their bactericidal activity and increasing periodontal destruction (Mealey and Oates, 2006; Stanko and Izakovicova Holla, 2014).

Additionally, macrophages also play a vital role in the pathogenesis of diabetes-associated periodontal diseases. An analysis of periodontitis patients with and without T2DM indicated that the M1/M2 macrophage ratio was significantly increased at the disease sites (Almubarak et al, 2020; Li et al, 2020b). Pro-inflammatory cytokines, such as IL-6 and TNF-α, can promote the polarization of macrophages towards the M1 phenotype (Wang et al, 2025). In patients with peri-implantitis, increased IL-6 levels, accompanied by senescent cell accumulation and higher SASP factor release, may interfere with the normal macrophage polarization. This results in M1-type macrophages remaining dominant and suppressing the tissue-repairing functions of M2-type macrophages, leading to impaired tissue regeneration around implants and sustained bone resorption.

Recently, studies have confirmed that DM and hyperglycemic conditions can induce changes in periodontal microbiota, thereby leading to periodontal tissue destruction (Bachtiar et al, 2021; Tang et al, 2022). In patients with peri-implantitis, an increase in senescent cells and the elevated release of SASP factors may interfere with the normal macrophage polarization. In peri-implantitis, microbial dysbiosis can lead to the excessive growth of pathogenic bacteria, increased inflammation, and progressive tissue destruction. Key pathogenic bacteria associated with peri-implantitis include Porphyromonas gingivalis, Tannerella forsythia, and Treponema denticola. Animal-based studies have confirmed that Porphyromonas gingivalis results in greater bone loss in peri-implantitis compared to healthy teeth (Tzach-Nahman et al, 2017).

Our study found that patients with T2DM-PI had more pronounced plaque accumulation compared to patients with common peri-implantitis. Excessive plaque not only evades the host's immune system and produces toxins that damage host tissues, but also exacerbates inflammation by inducing the release of inflammatory factors such as IL-1β and TNF-α (Deng et al, 2020), ultimately increasing the severity of peri-implantitis. For example, Yu et al (2022), revealed that DM may promote the progression of periodontitis by enhancing the bacterial network within the gingival tissue. However, at present, there are relatively few studies on the immune response and microbial changes in T2DM-PI. Further studies are needed to elucidate their role in disease progression.

Conclusion

In summary, this study shows that BMI, IL-1β, TNF-α, and MMP8 are independent risk factors for the development of T2DM-PI, with increased levels exhibiting a positive correlation with the severity of periodontal indicators. However,

the relatively small sample size and single-center design may introduce selection bias. Further investigations with a larger sample size and a prospective study design are required to validate these results and provide a more reliable basis for clinical diagnosis and treatment approaches.

Key Points

- Peri-implantitis is a biological complication of osseointegrated dental implants, and with the increasing use of implant-supported restorations, peri-implantitis has emerged as a significant concern for both clinicians and patients.
- The severity of peri-implantitis is linked to poor blood sugar control.
- Hyperglycemia and metabolic changes in diabetes promote cellular aging, and SASP serves as a key marker for this process.
- BMI, IL-1β, TNF-α, and MMP8 were identified as independent risk factors for peri-implantitis in the middle-aged group, whereas BMI was found to be an independent risk factor in the elderly group.
- IL-1β, TNF-α, and MMP8 were statistically correlated with PD in the M-DPI group, while IL-1β, MMP8, and RAGE were statistically associated with CAL.
- In the E-DPI group, MMP8 demonstrated a significant association with PD.

Availability of Data and Materials

All data included in this study are available from the corresponding authors upon reasonable request.

Author Contributions

WC designed the research study. WC and JQZ performed the research. JQZ provided help and advice on the experiments. SYC and JQZ analyzed the data and drafted the manuscript. All authors contributed to revising the manuscript critically for important intellectual content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the Second Affiliated Hospital of Zhejiang University School of Medicine (No. 2021-053), and all procedures complied with the Declaration of Helsinki. All patients provided informed consent.

Acknowledgement

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

References

Afrasiabi S, Heidari M, Younespour S, Chiniforush N. Evaluating the effect of mechanical debridement with adjunctive antimicrobial photodynamic therapy in comparison with mechanical debridement alone on the peri-implant parameters in type 2 diabetic mellitus patients with peri-implantitis: a systematic review and meta-analysis. BMC Oral Health. 2023; 23: 751. https://doi.org/10.1186/s12903-023-03337-9

Al-Aali KA, AlHelal A, Alhamoudi N, Alhenaki AM, Javed F, Abduljabbar T. Assessment of advanced glycation end products in the peri-implant sulcular fluid among moderate cigarette-smokers and non-smokers with peri-implantitis. Clinical Implant Dentistry and Related Research. 2020; 22: 380–386. https://doi.org/10.1111/cid.12917

Alassy H, Parachuru P, Wolff L. Peri-Implantitis Diagnosis and Prognosis Using Biomarkers in Peri-Implant Crevicular Fluid: A Narrative Review. Diagnostics. 2019; 9: 214. https://doi.org/10.3390/diagnostics9040214

Ali D, Baskaradoss JK, Joseph BK. Cortisol Levels in the Peri-implant Sulcular Fluid of Type-2 Diabetic and Non-diabetic Patients with Peri-implantitis. Oral Health & Preventive Dentistry. 2022; 20: 219–226. https://doi.org/10.3290/j.ohpd.b2960827

Almubarak A, Tanagala KKK, Papapanou PN, Lalla E, Momen-Heravi F. Disruption of Monocyte and Macrophage Homeostasis in Periodontitis. Frontiers in Immunology. 2020; 11: 330. https://doi.org/10.3389/fimmu.2020.00330

Armitage GC. Development of a classification system for periodontal diseases and conditions. Annals of Periodontology. 1999; 4: 1–6. https://doi.org/10.1902/annals.1999.4.1.1

Bachtiar BM, Theodorea CF, Tahapary DL, Astrella C, n/a N, Bachtiar EW. A pilot study of red complex and three genera subgingival microbiome in periodontitis subjects with and without diabetes, evaluated by MinION platform. F1000Research. 2021; 10: 79. https://doi.org/10.12688/f1000research.28216.4

Carcuac O, Derks J, Abrahamsson I, Wennström JL, Berglundh T. Risk for recurrence of disease following surgical therapy of peri-implantitis-A prospective longitudinal study. Clinical Oral Implants Research. 2020; 31: 1072–1077. https://doi.org/10.1111/clr.13653

Chai M, Zhang J, Meng Q, Liu A. Diagnostic Value of lncRNA XIST in Saliva for Early Peri-Implantitis. Oral Health & Preventive Dentistry. 2024; 22: 381–388. https://doi.org/10.3290/j.ohpd.b5656312

Chen Z, Hong Q. Correlation of serum IGF-1, AGEs and their receptors with the risk of colorectal cancer in patients with type 2 diabetes mellitus. Frontiers in Oncology. 2023; 13: 1125745. https://doi.org/10.3389/fonc.2023.1125745

Cortés-Vieyra R, Rosales C, Uribe-Querol E. Neutrophil Functions in Periodontal Homeostasis. Journal of Immunology Research. 2016; 2016: 1396106. https://doi.org/10.1155/2016/1396106

Darby I. Risk factors for periodontitis & peri-implantitis. Periodontology 2000. 2022; 90: 9–12. https://doi.org/10.1111/prd.12447

De Cecco M, Ito T, Petrashen AP, Elias AE, Skvir NJ, Criscione SW, et al. L1 drives IFN in senescent cells and promotes age-associated inflammation. Nature. 2019; 566: 73–78. https://doi.org/10.1038/s41586-018-0784-9

Delucchi F, Canepa C, Canullo L, Pesce P, Isola G, Menini M. Biomarkers from Peri-Implant Crevicular Fluid (PICF) as Predictors of Peri-Implant Bone Loss: A Systematic Review. International Journal of Molecular Sciences. 2023; 24: 3202. https://doi.org/10.3390/ijms24043202

Deng S, Hu Y, Zhou J, Wang Y, Wang Y, Li S, et al. TLR4 mediates alveolar bone resorption in experimental peri-implantitis through regulation of $CD45^{+}$ cell infiltration, RANKL/OPG ratio, and inflammatory

cytokine production. Journal of Periodontology. 2020; 91: 671–682. https://doi.org/10.1002/JPER.18-0748

Doğan ŞB, Kurtiş MB, Tüter G, Serdar M, Watanabe K, Karakış S. Evaluation of Clinical Parameters and Levels of Proinflammatory Cytokines in the Crevicular Fluid Around Dental Implants in Patients with Type 2 Diabetes Mellitus. The International Journal of Oral & Maxillofacial Implants. 2015; 30: 1119–1127. https://doi.org/10.11607/jomi.3787

Dubois SG, Tchoukalova YD, Heilbronn LK, Albu JB, Kelley DE, Smith SR, et al. Potential role of increased matrix metalloproteinase-2 (MMP2) transcription in impaired adipogenesis in type 2 diabetes mellitus. Biochemical and Biophysical Research Communications. 2008; 367: 725–728. https://doi.org/10.1016/j.bbrc.2007.12.180

Figueiredo LC, Bueno-Silva B, Nogueira CFP, Valadares LC, Garcia KMM, Filho GCDL, et al. Levels of Gene Expression of Immunological Biomarkers in Peri-Implant and Periodontal Tissues. International Journal of Environmental Research and Public Health. 2020; 17: 9100. https://doi.org/10.3390/ijerph17239100

Jansson L, Lundmark A, Modin C, Gustafsson A, Yucel-Lindberg T. Levels of matrix metalloproteinase-1 (MMP-1), MMP-2, MMP-3, osteopontin, pentraxin-3, and thymic stromal lymphopoietin in crevicular fluid samples from peri-implantitis, periodontitis, and healthy sites. Journal of Periodontal Research. 2025; 60: 473–483. https://doi.org/10.1111/jre.13338

Kageyama Y, Nakamura M, Igari Y, Yamaguchi S, Oguchi A, Murakawa Y, et al. Expression of matrix metalloproteinase-3 and -10 is up-regulated in the periodontal tissues of aged mice. Journal of Periodontal Research. 2022; 57: 733–741. https://doi.org/10.1111/jre.12996

Li Y, Teng D, Shi X, Qin G, Qin Y, Quan H, et al. Prevalence of diabetes recorded in mainland China using 2018 diagnostic criteria from the American Diabetes Association: national cross sectional study. BMJ (Clinical Research Ed.). 2020a; 369: m997. https://doi.org/10.1136/bmj.m997

Li Y, Wang X, Wang S, Zhu C, Guo J, Li K, et al. Complement 3 mediates periodontal destruction in patients with type 2 diabetes by regulating macrophage polarization in periodontal tissues. Cell Proliferation. 2020b; 53: e12886. https://doi.org/10.1111/cpr.12886

Li Z, Zhao Z, Chen S, Wang X, Wang D, Nie X, et al. Ge-Gen-Qin-Lian decoction alleviates the symptoms of type 2 diabetes mellitus with inflammatory bowel disease via regulating the AGE-RAGE pathway. BMC Complementary Medicine and Therapies. 2024; 24: 225. https://doi.org/10.1186/s12906-024-04526-x

Liang X, Liu L, Wang Y, Guo H, Fan H, Zhang C, et al. Autophagy-driven NETosis is a double-edged sword - Review. Biomedicine & Pharmacotherapy. 2020; 126: 110065. https://doi.org/10.1016/j.biopha.2020.110065

Mealey BL, Oates TW. Diabetes mellitus and periodontal diseases. Journal of Periodontology. 2006; 77: 1289–1303. https://doi.org/10.1902/jop.2006.050459

Milinkovic I, Djinic Krasavcevic A, Nikolic N, Aleksic Z, Carkic J, Jezdic M, et al. Notch down-regulation and inflammatory cytokines and RANKL overexpression involvement in peri-implant mucositis and peri-implantitis: A cross-sectional study. Clinical Oral Implants Research. 2021; 32: 1496–1505. https://doi.org/10.1111/clr.13850

Monje A, Pons R, Nart J, Miron RJ, Schwarz F, Sculean A. Selecting biomaterials in the reconstructive therapy of peri-implantitis. Periodontology 2000. 2024; 94: 192–212. https://doi.org/10.1111/prd.12523

Nibali L, Gkranias N, Mainas G, Di Pino A. Periodontitis and implant complications in diabetes. Periodontology 2000. 2022; 90: 88–105. https://doi.org/10.1111/prd.12451

Ok CY, Park S, Jang HO, Takata T, Lee OH, Bae MK, et al. FK866 Protects Human Dental Pulp Cells against Oxidative Stress-Induced Cellular Senescence. Antioxidants. 2021; 10: 271. https://doi.org/10.3390/antiox10020271

Puavilai G, Chanprasertyotin S, Sriphrapradaeng A. Diagnostic criteria for diabetes mellitus and other categories of glucose intolerance: 1997 criteria by the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (ADA), 1998 WHO consultation criteria, and 1985 WHO criteria. World Health Organization. Diabetes Research and Clinical Practice. 1999; 44: 21–26. https://doi.org/10.1016/s0168-8227(99)00008-x

Rajeev K, Karthika R, Mythili R, Krishnan V, Nirmal M. Role of receptors of advanced glycation end-products (RAGE) in type 2 diabetic and non-diabetic individuals with chronic periodontal disease: an immunohistochemical study. Journal of Investigative and Clinical Dentistry. 2011; 2: 287–292. https://doi.org/10.1111/j.2041-1626.2011.00079.x

Rajendran V, Uppoor A. A perspective on NETosis in diabetes and periodontal diseases. Journal of Indian Society of Periodontology. 2018; 22: 290–293. https://doi.org/10.4103/jisp.jisp_230_18

Rattanaprukskul K, Xia XJ, Hysa M, Jiang M, Hung M, Suslavich SF, et al. Dasatinib and Quercetin Limit Gingival Senescence, Inflammation, and Bone Loss. Journal of Dental Research. 2025; 104: 419–427. https://doi.org/10.1177/00220345241299789

Saito Y, Nodai T, Munemasa T, Mukaibo T, Kondo Y, Masaki C, et al. Diagnostic potential of endothelin-1 in peri-implant diseases: a cross-sectional study. International Journal of Implant Dentistry. 2024; 10: 32. https://doi.org/10.1186/s40729-024-00551-0

Song X, Yue Z, Fan L, Zou H, Zhao P, Nie L, et al. Relationship between circulating senescence-associated secretory phenotype levels and severity of type 2 diabetes-associated periodontitis: A cross-sectional study. Journal of Periodontology. 2023; 94: 986–996. https://doi.org/10.1002/JPER.22-0445

Stanko P, Izakovicova Holla L. Bidirectional association between diabetes mellitus and inflammatory periodontal disease. A review. Biomedical Papers of the Medical Faculty of the University Palacky, Olomouc, Czechoslovakia. 2014; 158: 35–38. https://doi.org/10.5507/bp.2014.005

Tang B, Yan C, Shen X, Li Y. The bidirectional biological interplay between microbiome and viruses in periodontitis and type-2 diabetes mellitus. Frontiers in Immunology. 2022; 13: 885029. https://doi.org/10.3389/fimmu.2022.885029

Teixeira QE, Ferreira DDC, da Silva AMP, Gonçalves LS, Pires FR, Carrouel F, et al. Aging as a Risk Factor on the Immunoexpression of Pro-Inflammatory IL-1β, IL-6 and TNF-α Cytokines in Chronic Apical Periodontitis Lesions. Biology. 2021; 11: 14. https://doi.org/10.3390/biology11010014

Tzach-Nahman R, Mizraji G, Shapira L, Nussbaum G, Wilensky A. Oral infection with Porphyromonas gingivalis induces peri-implantitis in a murine model: Evaluation of bone loss and the local inflammatory response. Journal of Clinical Periodontology. 2017; 44: 739–748. https://doi.org/10.1111/jcpe.12735

Wang P, Li Z, Song Y, Zhang B, Fan C. Resveratrol-driven macrophage polarization: unveiling mechanisms and therapeutic potential. Frontiers in Pharmacology. 2025; 15: 1516609. https://doi.org/10.3389/fphar.2024.1516609

Yang N, Nakagawa M, Nishiura A, Yamada M, Morikuni H, Honda Y, et al. Identification of Senescent Cells in Peri-Implantitis and Prevention of Mini-Implant Loss Using Senolytics. International Journal of Molecular Sciences. 2023; 24: 2507. https://doi.org/10.3390/ijms24032507

Yu Y, Kim HJ, Song JM, Kang J, Lee H, Park HR, et al. Differential microbiota network in gingival tissues between periodontitis and periodontitis with diabetes. Frontiers in Cellular and Infection Microbiology. 2022; 12: 1061125. https://doi.org/10.3389/fcimb.2022.1061125

Yuan S, Wei Y, Jiang W, Sun F, Li S, Li Q, et al. CCR2 is a potential therapeutic target in peri-implantitis. Journal of Clinical Periodontology. 2024; 51: 354–364. https://doi.org/10.1111/jcpe.13916

Zeidán-Chuliá F, Yilmaz D, Häkkinen L, Könönen E, Neves de Oliveira BH, Güncü G, et al. Matrix metalloproteinase-7 in periodontitis with type 2 diabetes mellitus. Journal of Periodontal Research. 2018; 53: 916–923. https://doi.org/10.1111/jre.12583