BJBMB

Biobacta Journal of Biochemistry and Molecular Biology

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Original article

Salivary Chemerin as an Inflammatory Biomarker Associated with Dental Caries Susceptibility in Patients with Type 2 Diabetes Mellitus

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DOI: https://doi.org/10.71428/BJBMB.2026.0111

ABSTRACT

Background: Type 2 Diabetes Mellitus (T2DM) has a significant association with oral health problems such as dental caries. Chemerin is an adipokine involved in metabolic and inflammatory conditions. **Aim of the study**: This study aims to explore the possible significance of salivary chemerin as an inflammatory biomarker linked to dental caries susceptibility in T2DM patients. **Methods**: The study used a cross-sectional study design to recruit 90 subjects grouped into three groups: Group 1 (Healthy Controls, n=20); Group 2 (T2DM patients with low caries, n=42); and Group 3 (T2DM patients with severe caries, n=28). Anthropometric and biochemical parameters like Body Mass Index (BMI), glycated hemoglobin (HbA1c), Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), and Decay, Missing, Filling Teeth Index (DMFT) were measured. Salivary chemerin levels were determined by the ELISA. **Results:** Chemerin levels in saliva were found to be markedly higher in patients with type 2 diabetes mellitus (T2DM) with a diagnosis of severe dental caries (5.42 ± 1.10 ng/mL) than in T2DM patients with mild dental caries (3.80 ± 0.95 ng/mL) and normal subjects (1.15 ± 0.40 ng/mL) ($P < 0.001$). Positive relationships have been noted between serum Chemerin concentrations and the degree of HbA1c, along with DMFT score. Furthermore, BMI showed a positive relationship with salivary Chemerin concentrations and dental caries.

Conclusion: Salivary chemerin can be used as a reliable marker of inflammation associated with the risk of dental caries development among T2DM patients. The findings indicate that dental cavities emerge due to a combination of metabolic dysfunction and inflammation.

Keywords: Salivary Chemerin, Type 2 Diabetes Mellitus, Dental Caries Susceptibility, Inflammatory Biomarkers, DMFT Index, Insulin Resistance.

1. INTRODUCTION

Insulin is a peptide hormone produced by the beta cells of the pancreas. Insulin plays a crucial role in controlling blood sugar levels through facilitating glucose uptake in cells and managing carbohydrate, fat, and protein metabolism. Insulin also possesses mitogenic activity involved in cell proliferation (1).

Insulin resistance can be described as a state in which the body fails to respond effectively to

Received: March 12, 2026. Accepted: May 18, 2026. Published: June 18, 2026

insulin, leading to disruption of one or more biological functions of insulin (2). It has been implicated as a precursor to developing type 2 diabetes and increases the likelihood of heart disease (3,4).

Type 2 diabetes mellitus (T2DM) represents a global health problem because many people suffer from this condition. It involves chronically high levels of blood glucose, low insulin sensitivity, and the development of dysfunctional pancreatic beta cells. Additionally, diabetes can be considered a group of conditions that negatively affect many organs in the human body (5,6).

Type 2 diabetes mellitus should be regarded as a condition related to the low body response to insulin (7). Formerly known as non-insulin-dependent or adult-onset diabetes, it currently represents the most common type of diabetes (8). It has been shown that diabetes can affect the development of periodontal disease; therefore, T2DM is usually associated with an increased risk of developing periodontitis (9). Due to the poor ability to cope with the inflammation response, high levels of inflammatory cytokines can be observed (10).

Chemerin is a multifunctional signaling molecule that is coded in the RARRES2 gene. It is initially expressed as an inactive proprotein of 143 amino acids, referred to as prochemerin (11).

It is processed to the active form through the action of specific enzymes, referred to as serine proteases, which remove the C-terminus to give the active molecule. Chemerin is present in saliva and gingival crevicular fluid, with levels increasing alongside the severity of inflammation and the metabolic deterioration seen in diabetic patients (12).

Chemerin may contribute to periodontal tissue deterioration by increasing the expression of pro-inflammatory cytokines and matrix metalloproteinases. The effect of non-surgical periodontal therapy on chemerin levels was considerably decreased in levels of chemerin at 6 months compared to the baseline values (13).

Dental caries is a multifactorial microbial disease, and salivary chemistry is crucial in balancing demineralization and remineralization. Elevated salivary sugar in diabetic patients disrupts this balance through two primary pathways (14).

1. Ecological Shift: High levels of glucose and fructose in saliva selectively promote the growth of cariogenic bacteria like *Streptococcus mutans*, while reducing the abundance of health-associated species such as *Streptococcus sanguinis*. This shift makes the dental plaque more acidogenic and acid-tolerant.
2. Reduced Flow and Buffering: Diabetes often leads to xerostomia (dry mouth) and a reduced salivary flow rate. This limits the ability of saliva to neutralize acids produced during sugar metabolism.

2. Materials and Methods

2.1. Study Design and Participants

The current study adopts an observational case-control approach, using a sample size of 90 subjects who were between the ages of 22 and 55 years. The subjects for this study were randomly selected among patients who visited the specialized dentistry clinics at Al-Kafeel University in the period from October 2025 to January 2026. Subjects' informed consent was acquired prior to participating in the experiment after being introduced to the study objective. The study was approved by the Ethics Committee of the College of Dentistry, Al-Kafeel University.

Groups:

1) Group 1: Healthy Controls (n=20) – people who are systemically healthy without a history of diabetes and who have a low level of caries.

2) Group 2: T2DM with Low Caries (n=42)—people who have a history of type 2 diabetes mellitus for at least one year, along with a low level of DMFT (≤ 6).
3) Group 3: T2DM with Severe Caries (n=28)—people who have a history of type 2 diabetes mellitus along with a severe level of dental caries, DMFT ≥ 10.

Exclusion criteria included pregnancy, smoking, current orthodontic treatment, and the presence of other systemic inflammatory diseases.

2.2. Anthropometric and Glycemic Assessment

The Body Mass Index (BMI) was calculated for all the participants, which is the ratio of the body weight in kilograms to the square of the height in meters (kg/m²). For the biochemical analysis, venous blood samples were drawn after an 8-hour fasting period. Fasting Blood Sugar (FBS) and Random Blood Sugar (RBS) levels were measured using an automated glucose analyzer. Glycemic control was measured in the form of HbA1c levels. Insulin resistance was measured in the form of the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), which is the product of fasting insulin (in μU/mL) and fasting glucose (in mg/dL) / 405.

2.3. Salivary Collection and Chemerin Analysis

Unstimulated saliva samples, each measuring 2 mL in volume, were obtained from subjects in the morning, in the time frame of 9:00 to 11:00 hours, to minimize interdaily variations. The subjects were asked to refrain from eating, drinking, and conducting oral hygiene activities for two hours before the collection. Subjects were asked to swallow the saliva and then lean their heads in such a manner that would allow saliva to drain. The samples obtained were then centrifuged at 3000 rpm for 15 minutes at 15°C, and the obtained precipitates were frozen at -20°C until used for measurements. Saliva chemerin levels were measured using a commercial ELISA kit.

2.4. Clinical Dental Examination

A single calibrated examiner performed the intraoral examinations under standard dental light. Dental caries status was assessed using the DMFT Index (Decayed, Missing, and Filled Teeth), following the World Health Organization (WHO) diagnostic criteria. Caries susceptibility was determined based on the cumulative score of the index.

2.5. Statistical Analysis

Data were analyzed using SPSS software (Version 26.0). Descriptive statistics were expressed as Mean ± standard deviation (SD). One-way Analysis of variance (ANOVA) was used to compare continuous variables among the three groups, followed by Tukey's post-hoc test for multiple comparisons. An independent sample t-test and Pearson's correlation coefficient were applied to evaluate the relationship between salivary chemerin and other clinical parameters. A P-value of < 0.05 was considered statistically significant ($P > 0.05$ = non-significant). The concentration of chemerin was estimated utilizing an enzyme-linked immunosorbent assay (ELISA).

3. Results

3.1. General Characteristics and Metabolic Profile

Overall, there were 90 participants in the study who underwent clinical examination. These participants were divided into three groups, namely Group 1, which comprises Healthy Controls (n=20), Group 2, which was comprised of Type 2 Diabetes Mellitus (T2DM) with Low Caries (n=42), and Group 3, T2DM with Severe Caries (n=28). The differences in age among all the groups were not statistically significant ($P = 0.112$). On the other hand, BMI was found to be significantly higher among Group 3 participants, which was 30.6 ± 1.2 kg/m², compared

to those in Group 2, which was 26.8 ± 0.9 kg/m², and 22.1 ± 1.4 kg/m² in the control group (P < 0.001).

3.2. Glycemic Status and Insulin Resistance

There was a marked disturbance in glycemic control among diabetic participants compared with healthy subjects. The maximum level of hemoglobin A1c (HbA1c) value was recorded for Group 3 (9.1 ± 1.2%), which is significantly greater than the corresponding value for Group 2 (7.6 ± 0.8%) and Group 1 (5.2 ± 0.4%) (P < 0.001). Likewise, there was an increase in insulin resistance, measured using the HOMA-IR index, from the mild caries to the severe caries group; the severe caries group had a higher value compared with that of the mild group and the control group (P < 0.001) (Table 3.1).

3.3. Salivary Chemerin Levels and Dental Caries

Levels of salivary chemerin increase as the dental caries increase in severity. On average, the level of chemerin is higher in Group 3 (5.42 ± 1.10 ng/mL) than that of Group 2 (3.80 ± 0.95 ng/mL), while the level of chemerin is lowest for the healthy controls (1.15 ± 0.40 ng/mL). The difference is significant at P < 0.001. The increase is also seen with the DMFT Index, as the values increase for Group 3 (14.8 ± 3.5), decrease for Group 2 (6.4 ± 2.2), and continue to decrease for Group 1 (2.1 ± 1.0). This shows that salivary chemerin has the potential to be an effective inflammatory marker for dental caries susceptibility for individuals with type 2 diabetes, as shown in Table 1.

3.4. Comparison of Clinical and Biochemical Parameters Among Study Groups

A one-way Analysis of variance (ANOVA) was conducted to compare the mean differences of BMI, glycemic parameters, insulin resistance index, salivary chemerin levels, and DMFT scores among the three study groups:

- Healthy controls (n=20)
- T2DM with low caries (n=42)
- T2DM with high caries (n=28)

Table (1): Comparison of Mean ± SD Among Study Groups

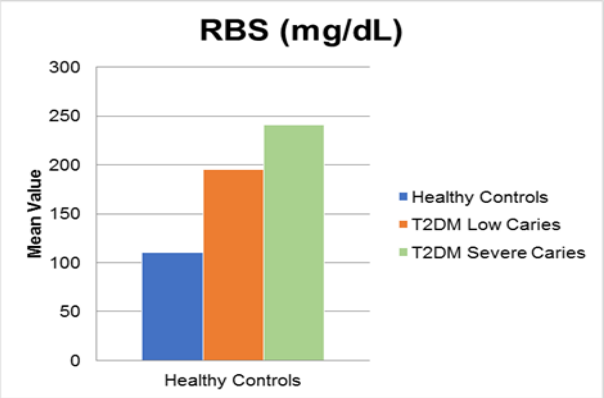
Comparison of Clinical Parameters Across Groups				
Variable	Group 1: Healthy Controls (n=20)	Group 2: T2DM - Low Caries (n=42)	Group 3: T2DM Severe Caries(n=28)	P-value
BMI	22.2 ± 1.33	26.76 ± 0.82	30.53 ± 1.02	0.0*
FBS	88.85 ± 2.78	143.45 ± 3.9	173.14 ± 6.6	0.0*
RBS	111.7 ± 5.1	197.07 ± 7.2	250.86 ± 14.15	0.0*
HbA1c	5.17 ± 0.27	7.57 ± 0.39	9.29 ± 0.59	0.0*
HOMA-IR	1.2 ± 0.2	3.9 ± 0.27	5.78 ± 0.47	0.0*
Chemerin	1.19 ± 0.2	3.76 ± 0.38	5.64 ± 0.51	0.0*
DMFT	2.0 ± 1.34	6.62 ± 1.23	14.46 ± 2.19	0.0*

As shown in Table 1, there is a significant difference (p = 0.0) among the means of the parameters measured in the laboratory tests in the three caries severity classes (refer to Table 1). The comparisons of the parameters tested were done between the patients with mild and severe test results for fasting and random serum glucose, HbA1c, insulin resistance, serum Chemerin, and DMFT level. The results obtained were:

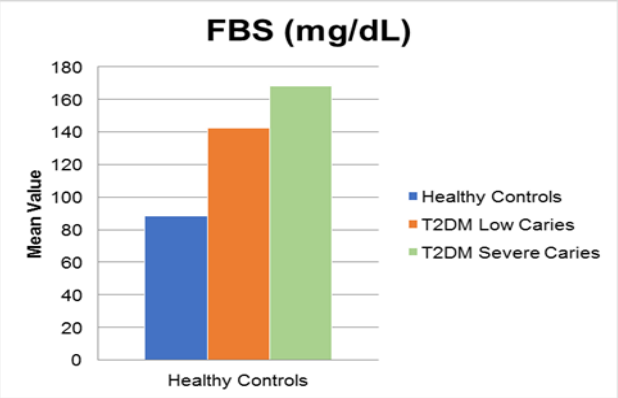
- Fasting serum glucose: 88.85 ± 2.78, 143.45 ± 3.9, 173.14 ± 6.6

- Random serum glucose: 111.7 ± 5.1, 197.07 ± 7.2, 250.86 ± 14.15
- HbA1c: 5.17 ± 0.27, 7.57 ± 0.39, 9.29 ± 0.59
- Insulin resistance: 1.2 ± 0.2, 3.9 ± 0.27, 5.78 ± 0.47
- Serum Chemerin: 1.19 ± 0.2, 3.76

The outcomes obtained from the graph (Schemes A-H) demonstrate a strong positive relationship between metabolic disorder and poor oral health. More precisely, along with increases in FBS, RBS, HbA1c, and HOMA-IR levels, one can observe an upward trend in the intensity of caries (DMFT) and the amount of chemerin. The analysis of these correlations proves that poor glucose homeostasis, insulin resistance, and systemic inflammation significantly correlate with caries frequency in the examined cohorts.



scheme (A)



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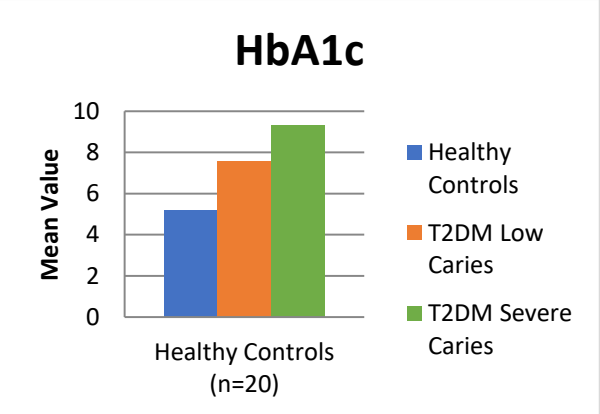
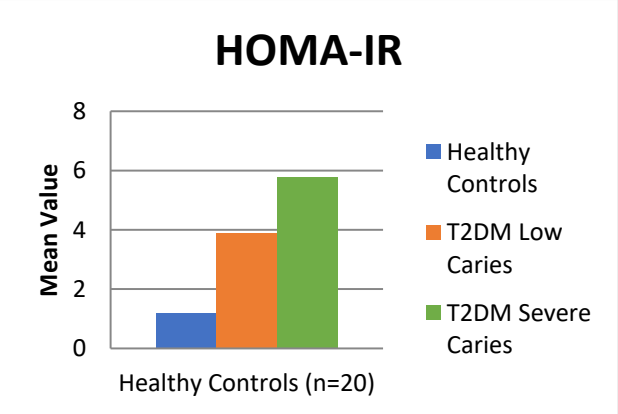


Scheme (C)



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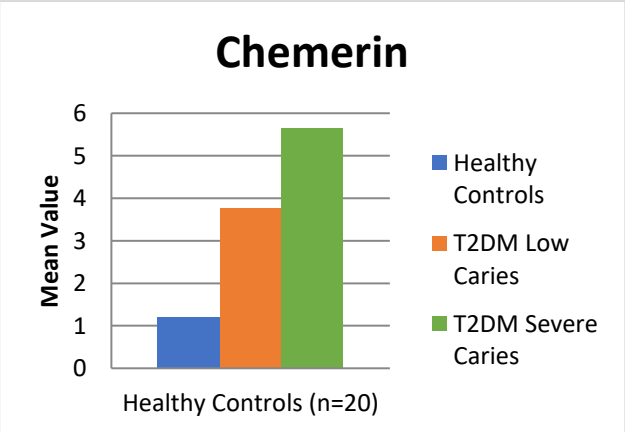
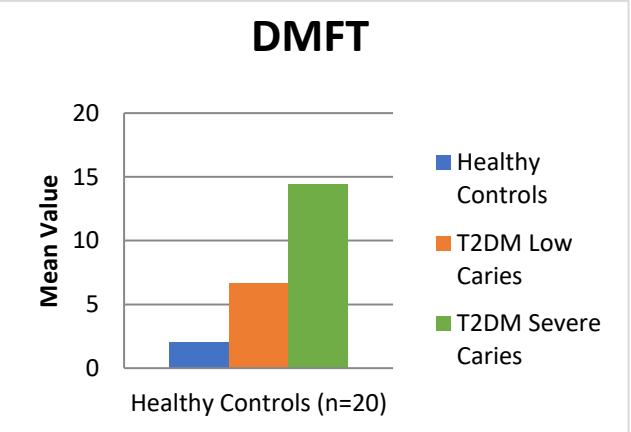
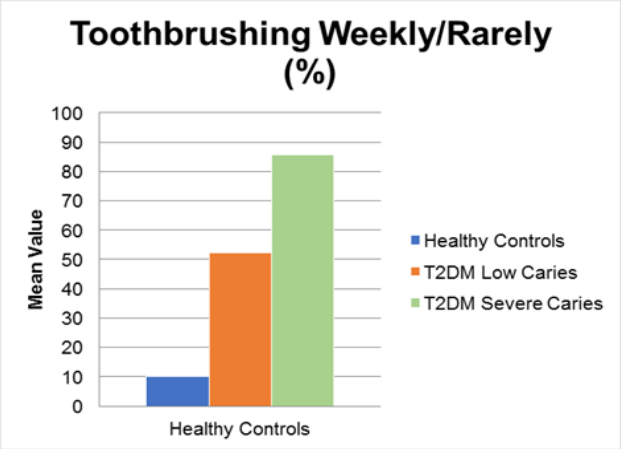
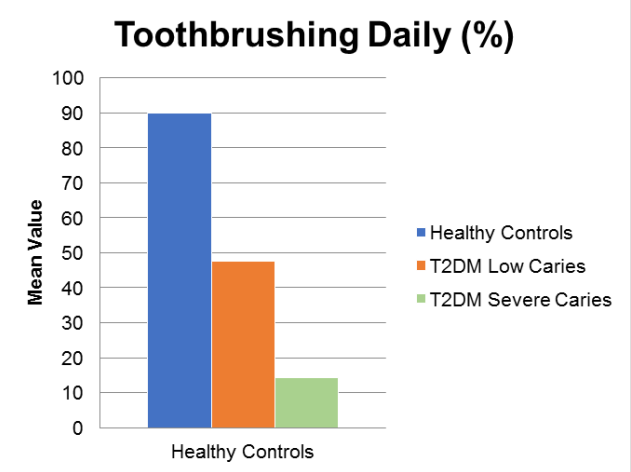






Scheme (G)



Scheme (H)

It can be seen from the data available in Schemes (A - H) that there is a notable relationship between metabolic condition, systemic inflammation, and dentistry. In this context, it is clear that the "T2DM Severe Caries" group shows the maximum level of metabolic abnormality, which is represented by higher levels of FBS, RBS, and HbA1c.

ANOVA revealed highly statistically significant differences ($P < 0.001$) among the three groups for all studied parameters. There was a progressive increase from healthy individuals to diabetic patients with high caries in:

- Glycemic parameters (FBS, RBS, HbA1c)
- Insulin resistance (HOMA-IR)
- Salivary chemerin levels
- Caries severity (DMFT)

This indicates a strong metabolic-inflammatory gradient across the groups.

3.5. Post Hoc Analysis (Tukey Test) for Salivary Chemerin

A Tukey HSD post hoc test, as shown in Table 3.2, was performed to determine pairwise differences in salivary chemerin levels between groups.

The Tukey test showed statistically significant differences between all groups.

- Chemerin levels were significantly higher in T2DM patients compared to healthy controls.
- Patients with high caries showed significantly higher chemerin levels compared to those with low caries.

This confirms that salivary chemerin increases progressively with both metabolic dysregulation and caries severity.

The ROC curve analysis in Table 3-3 and Figure 1 was conducted to evaluate the diagnostic performance of several biomarkers. The results demonstrated exceptional diagnostic accuracy for the studied parameters:

In the table 3.3, we show the following:

- **Chemerin and HOMA-IR**: Both biomarkers exhibited perfect diagnostic precision with an Area Under the Curve (AUC) of **1.0** (95% CI: 1.0–1.0).
- **HbA1c**: This marker showed near-perfect diagnostic capability with an AUC of **0.998** (95% CI: 0.9904 – 1.0056).
- **BMI**: While recording the lowest AUC among the group at **0.865** (95% CI: 0.789 – 0.941), it still represents a very strong and statistically significant predictive value.

The Receiver Operating Characteristic (ROC) curve test is performed, and its results are shown in Table 3-4 and Figure 1 to evaluate the diagnostic value of chemerin in distinguishing patients with dental caries (DMFT). In this case, the discriminative ability obtained by the ROC curve test showed very good discrimination, with an Area Under the Curve (AUC) of 0.994 (95% confidence interval: 0.98–1.00).

Based on these findings, it can be inferred that chemerin is a reliable marker for distinguishing patients with dental caries from those without.

- **AUC (0.994):** The Area Under the Curve value of **0.994** indicates **excellent diagnostic accuracy**, demonstrating the test's superior ability to distinguish between the study groups.
- **95% CI (0.98 – 1.00):** The 95% confidence interval suggests high statistical reliability and precision of the AUC estimate.
- **Cut-off (1.15):** The optimal threshold for classification is **1.15**; values exceeding this point are predictive of the target condition.
- **Sensitivity (97%):** The test shows a **97%** probability of correctly identifying true positive cases (the diseased group).
- **Specificity (96%):** The test shows a **96%** probability of correctly identifying true negative cases (the healthy group).

The optimal cutoff value of Chemerin was determined using Youden's index and found to be approximately 1.15, which provided a sensitivity of 97% and specificity of 96%.

Table (3.2): Tukey Post Hoc Comparison for Chemerin

Comparison	Mean Difference	P-value	Significance
Healthy vs Low Caries	Significant ↑	<0.001	Significant
Healthy vs High Caries	Highly Significant ↑	<0.001	Significant
Low Caries vs High Caries	Significant ↑	<0.001	Significant

Table 3.3: The ROC curve analysis.

Biomarker	AUC	95% CI
Chemerin	1.0	1.0 - 1.0
HOMA-IR	1.0	1.0 - 1.0
HbA1c	0.998	0.9904 - 1.0056
BMI	0.865	0.789 - 0.941

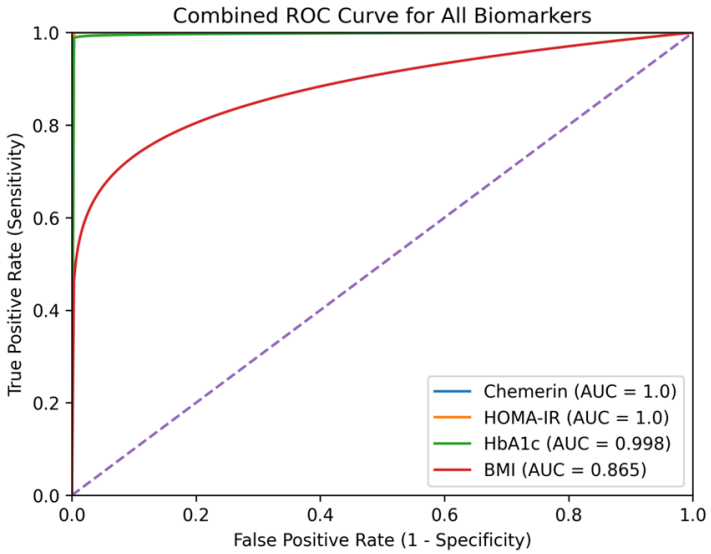


Fig. 1: The ROC curve for all parameters

Table 3.4: Receiver Operating Characteristic (ROC) curve of Chemerin.

Parameter	Value
AUC	0.994
95% CI	0.98 – 1.00
Cut-off	1.15
Sensitivity / Specificity	97% / 96%

4. Discussion

Clinical evidence suggests parallel changes in both Chemerin and salivary sugars, with an especially clear relationship in cases of periodontal disease. This parallel increase coincides with a rise in the DMFT index and substantiates the assumption regarding the role of salivary chemerin as a biological marker indicating the intensity of metabolic and immunological stresses within the mouth.

The connection between Chemerin and caries is due to the action of Chemerin in immune reactions under conditions of excess sugars and microbial infection. The molecule acts as part of the innate immunity and is produced endogenously as part of saliva in a concentration of 1.3 ± 0.5 ng/mL of total proteins.

Dental caries is a complex microbiological disease, wherein saliva plays a key role in balancing tooth enamel demineralization and remineralization. In the case of increased sugar content due to diabetes, two phenomena are altered (14).

1. Ecological shift: If there's a lot of glucose and fructose in the saliva, the cavity-causing bacteria, such as Streptococcus mutans, thrive, causing the beneficial bacteria, such as *Streptococcus sanguinis*, to disappear, which makes the plaque more difficult to neutralize.
2. Reduced flow and buffering: Dry mouth, which is common in diabetes, reduces the flow of saliva, which makes the saliva less effective in the neutralization of the acid produced by the sugars in the mouth, as shown by the fact that better control of blood glucose levels, which means less glucose transferred from the blood to the saliva, leads to a better balance of the oral microbiome.

This research highlights the clear connection between salivary chemerin, glucose, and tooth decay. In particular, increased glucose levels in the bloodstream are accompanied by an increased amount of glucose and fructose in saliva, which makes bacteria responsible for tooth decay more active. Higher activity of cariogenic bacteria results in a lowered pH level in saliva and increased production of chemerin due to the activation of inflammation processes.

According to Magán, as in (15), the concentration of chemerin is notably higher in people who experience chronic inflammatory processes in the mouth area. Therefore, a positive correlation exists between the concentration of salivary chemerin and dental inflammation and periodontal injury experienced by patients with metabolic disorders. The Özkan, as in (16), notes that salivary chemerin can be used as a general inflammatory marker of systemic inflammation and is correlated with BMI; still, salivary chemerin cannot be considered a specific biomarker of tooth decay since its concentration depends on gingival health and adiposity.

This metabolic state also exhibits elevated insulin resistance (HOMA-IR) and increased chimerin concentration, a known inflammatory adipokine. These systemic indicators directly impact oral health, as evidenced by the higher DMFT scores within this group. Furthermore, a significant variation in hygiene practices was observed; while approximately 90% of healthy individuals brush their teeth daily, this rate drops considerably in the severe caries group, with approximately 85% reporting weekly or infrequent brushing. Taken together, these findings suggest that the synergy between uncontrolled type 2 diabetes, systemic inflammation, and poor oral hygiene significantly exacerbates the severity of dental caries.

5. Conclusion

To sum up, this study shows an obvious positive relationship between the level of Chemerin in saliva and the degree of dental caries in T2DM subjects. In addition, this study reveals the potential role of Chemerin as an inflammatory marker in the development of oral diseases, thus emphasizing the importance of the oral aspect during the treatment and care of diabetic patients. Prevention of severe tooth decay is highly necessary in this group.

It should be noted that even though these results reveal the usefulness of using Chemerin as a biomarker for evaluating the degree of disease severity, it should be considered that the presence of systemic inflammation in diabetic patients can affect the obtained results and thus decrease the level of accuracy. Thus, further investigation is needed to identify whether Chemerin in saliva can be considered an indicator for direct consequences of caries or a result of systemic inflammation due to T2DM and oral infections. For this purpose, it is suggested to use the test results in routine examinations of diabetic patients' oral cavity to prevent infections.

It is additionally important to state that, apart from being secreted in adipose tissues, the secretion of chemerin is also observed in salivary glands and oral epithelial tissues under the stimulation caused by cariogenic bacteria in the case of inflammation. Nevertheless, chronic hyperglycemia, which is typical of diabetes, along with the persistence of inflammation, changes the effect of chemerin from positive to negative as a result of the action of oxidative stress and advanced glycation end-products (AGE). Consequently, appropriate treatment of diabetes through effective glycemic control, accompanied by periodontal therapy, appears to be the most effective method for the reduction of chemerin concentrations in saliva and improvement of glycemic dynamics and prevention of fast tooth decay observed in diabetes patients.

Conflict of interest: NIL

Funding: NIL

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