The Correlation between Resistin with Metalloproteinase-8, and Vitamins A, C, D, E among Patients Having Stage III Periodontitis

Jehan Abdulwahab Mohammad*

Abstract

Resistin, a hormone secreted by adipose tissue and immune cells, has a key role in the diagnosis and treatment of many inflammatory and metabolic disorders. However, the precise role of resistin in the human body remains to be studied further. Sixty-seven individuals were involved in this study and divided into 2 groups: 36 patients with stage III periodontitis (case group) and 31 healthy individuals (control group). In addition to their ages, sexes, and body mass index, serum levels of resistin and vitamins A, C, D, and E, as well as salivary matrix metalloproteinase-8, were measured. There was no significant difference in age, gender, or BMI between the study groups. However, the levels of resistin, vitamins A, C, D, and E, and MMP-8 were significantly different. Furthermore, resistin had a strong and significant negative correlation with vitamin C, a moderate and significant negative correlation with vitamin A, and a moderate and significant positive correlation with salivary metalloproteinase-8. The study demonstrated that resistin has strong prognostic value in stage III periodontitis.

Keywords: Antioxidant vitamins, Metalloproteinase-8, Periodontitis, Resistin

Introduction

Chronic inflammation of the tissues that support teeth is called periodontitis. The problem of oral health is becoming more widespread. Periodontal diseases have been linked to several microbes, which trigger an immune response that leads to a cascade of inflammatory responses to pathogens in tooth plaque (Fischer, 2020; Dannewitz et al., 2021). The primary objective of periodontal treatment is to maintain microbial stability and reduce bacterial load, thereby creating a microbiome that promotes periodontal health (ElKenawy et al., 2023; Bouh et al., 2024; Islam et al., 2024; Lopez-Ramos et al., 2024; Noor et al., 2024; Samaranayake et al., 2024; Gurung & Rai, 2025; Liedekerke et al., 2025). These changes result in a relatively stable level of periodontal attachment and reduced gingival inflammation (Elmeligy et al., 2024). Stage III periodontitis, also known as severe periodontitis with the possibility for future tooth loss, is a serious gum disease characterized by extensive damage to the teeth's attachment apparatus, which may result in tooth loss (Saleh & Katz, 2021).

Periodontitis has been linked to various systemic disorders, including diabetes and cardiovascular diseases. However, there are other variables that affect the development of periodontal problems and are linked to periodontitis (Liccardo et al., 2019). Cell-signalling molecules called adipokines are located around internal organs (visceral fat) and beneath the skin (subcutaneous fat). Moreover, other immune cells, particularly macrophages, support the synthesis of adipokines. Resistin, also known as adipocyte-derived secreted factor (ADSF), is a proinflammatory adipokine involved in many immunological and inflammatory conditions. Human resistin is primarily produced by monocytes and macrophages, which are present in peripheral blood vessels and adipose tissue (Devanoorkar et al., 2014). Although the exact molecular mechanism linking resistin and periodontitis remains unknown, it is understood that periodontitis is linked to an increase in the production of proinflammatory mediators, which may stimulate proinflammatory adipokines like resistin release (Devanoorkar et al., 2014).

On the other hand, the periodontal pathogen bacteria found in tooth plaque activate host cells and generate cytokines. Polymorphonuclear (PMN) cells are absorbed by these cytokines and enter the infection site. PMNs use reactive oxygen species (ROS) and proteolytic enzymes to combat infections. Periodontitis is directly linked to an increase in ROS molecules. The antioxidant defence system in the human body works to neutralize ROS and convert them into less potent forms. Vitamins A, C, D and E are present in this system (Dahiya et al., 2013). Vitamin A is a set of fat-soluble compounds, including 3,4-dehydroretinol, 3-hydroxyretinol, retinal, and retinol. Plants contain around 50 kinds of carotenoids, lipid-soluble pigments that act as precursors to vitamin A. Retinoic acid, a physiologically active form of vitamin A, helps maintain mucosal tissues and regulate cell development, including immune cells (Hans et al., 2023).

Vitamin C is an essential vitamin that has reducing and antioxidant properties, scavenges free radicals, and functions as a cofactor for an enzyme in cells. Furthermore, by encouraging the production of periodontal ligament progenitor cells, vitamin C helps to prevent and delay the progression of periodontal disease (Tada & Miura,

Jehan Abdulwahab Mohammad*
Department of Pharmacognosy and Medicinal Plants, College of Pharmacy, University of Mosul, Mosul, Iraq.

*E-mail: dr.jehan.biochem@uomosul.edu.iq

2019). Vitamin D is required to sustain the immune system and regulate calcium and phosphorus metabolism. This fat-soluble vitamin is present in certain foods and supplements, and it can also be produced by the skin when exposed to sunlight. Vitamin D has a preventive benefit in several illnesses, such as cancer, coronary heart disease, and diabetes mellitus, by modulating the inflammatory response (Jeon & Shin, 2018; de la Guía-Galipienso et al., 2021) . Inadequate vitamin D intake can lead to decreased bone mineralization, a negative calcium imbalance, and bone structural degradation. Insufficient vitamin D causes rickets in children and osteoporosis in adults (Kennel et al., 2010). Vitamin E is the primary fat-soluble antioxidant in the body. The exact role of vitamin E in the management of periodontitis is up for discussion (Behfarnia et al., 2021). In an effort to identify reliable biomarkers from saliva and gingival crevicular fluid for the diagnosis of periodontitis, oral fluids have been thoroughly studied. One of the biomarkers that has been studied the most is metalloproteinase-8 (MMP-8). MMP-8 levels in oral fluids can be used in noninvasive methods to identify active periodontal tissue degeneration (Sorsa et al., 2020). In patients with stage III periodontitis, the study intends to evaluate the function of resistin as an inflammatory mediator and its relationship to vitamins A, C, D, E, and metalloproteinase-8.

Materials and Methods

Patients

The target population consisted of individuals with severe periodontitis who were diagnosed with stage III periodontitis according to the latest definition (Caton et al., 2018). The Collegiate Committee for Medical Research Ethics gave ethical committee approval code: (CCMRE-phA-25-12). This case-control research was carried out in a private laboratory. Additionally, Dr Ahmad Kharoofa's private dentistry clinics provided patient samples (Meneses-La-Riva et al., 2023; Szklener et al., 2023; García et al., 2024; Hodoșan et al., 2024; Tanaka et al., 2024; Adams & Hayes, 2025; Kunie et al., 2025; Wei & Huang, 2025). The research approach, including the questionnaire, laboratory investigation, and clinical assessment, was thoroughly explained to each participant. Patients who agreed to continue the study then gave their informed consent to participate. Our study process began with a questionnaire, and the names of patients, age, gender, weight, height, and medical history were among the information it contained. The study period lasted from June 2025 to October 2025, which included 67 subjects split into 2 groups: the case group, which included 36 patients diagnosed with stage III periodontitis, and the control group, which comprised 31 healthy volunteers matched by age, sex, height, and weight with the case group. Participants in this study ranged in age from 35 to 55.

Control group with the following criteria: no symptoms of bone loss, clinical attachment loss (CAL), or systemic infection, and the individual is not currently using any drugs. Probing pocket depth (PPD) of at least 3 mm. Less than 10% of the mouth made up of bleeding on probing (BOP) was used on the individuals in the control group.

Participants who had taken oral contraceptives, immunosuppressive drugs, antibiotics, or anti-inflammatory drugs within three months prior to the start of the study were excluded.

Additionally, women with diabetes and those who were pregnant or lactating were not included. In addition, patients were excluded if they were taking vitamin D-containing multivitamins or food supplements, or if they had previously taken drugs that included corticosteroids, anticonvulsants, channel blockers, bisphosphonates, calcium phenytoin, or cyclosporine that affected bone, mineral metabolism and periodontal health. Finally, the study didn't include individuals with chronic diarrhoea or a malabsorption condition.

Anthropometric Measures

A German weight scale (Beurer) was used to measure the participants' body weight while they were on an empty stomach, dressed in loose clothes, and without shoes. Participants had to stand straight with their heads horizontal, legs together, and back, buttocks, and heels in contact with the wall to have their heights measured. The body mass index was calculated by dividing the weight (in kilograms) by the height (in square meters) (Mohajan & Mohajan, 2023).

Periodontal Examination

Comprehensive full-mouth periodontal and radiographic examinations were conducted independently by a qualified dentist. Measurements of PPD of 6mm or more, CAL of 5mm or more, and missing teeth due to periodontitis are four or fewer. Additionally, plaque index (PI), gingival index (GI), and BOP were taken into consideration when diagnosing stage III periodontitis. Both PPD and CAL were measured using a graduated William's periodontal probe. The findings were collected from six areas per tooth: mesio-buccal, mid-buccal, disto-buccal, mesio-lingual, mid-lingual, and disto-lingual. PPD was measured in millimetres at six preset places, between the base of the gingival sulcus and the free gingival margin. The mean PPD for each tooth is calculated by averaging readings from the six places surrounding it. CAL was measured at six predetermined places around each tooth, from the base of the pocket to the cementoenamel junction (Caton et al., 2018).

Clinical Laboratory Analysis

A disposable syringe was used to draw blood from each participant's vein. Before serum was separated by centrifugation at 3,000 rpm for 10 minutes, blood was allowed to clot at room temperature. The serum was split into two Eppendorf tubes and stored at -20°C before measurement.

According to the manufacturer's instructions, resistin was measured using the first Eppendorf tube using a human RETN (resistin) ELISA kit (Elabscience®, USA). An ELISA reader (BIO-TEK, USA) was used to quantify optical density at 450 nm using the colorimetric technique. The sensitivity of the test was 0.0187 ng/mL.

Vitamins A, C, D, and E are measured in the second Eppendorf tube using a colorimetric ELISA Kit (Elabscience®, USA). Vitamin A was tested at a detection range of 15.63-1000 ng/mL,

an optical density of 450 nm ± 2 nm, and a sensitivity of 9.38 ng/mL in accordance with the manufacturing instructions for competitive-ELISA kits. While for vitamin C measurement, the detection range of 0.31-17.5 µg/mL, optical density of 536 nm, and kit's sensitivity of 0.31 µg/mL was used, vitamin D was measured at detection range of 6.25-400 ng/mL, optimal density of 450 nm ± 2 nm, and kit's sensitivity of 3.75 ng/mL, but for vitamin E measurement, the detection range of 0.09-40 µg/mL, optical density of 533 nm, and the kit's sensitivity of 0.09 µg/mL was used. By comparing the optical density of the resultant solution to the standard curve, the content of vitamins A, C, D, and E was determined.

For salivary secretion, the study participants had to fast for 2 hours before the exam. Navazesh's approach was used to collect about 3 ml of unstimulated and entire expectorated saliva from each subject and deposit it in sterile 5 ml saliva tubes. Samples were kept at -80°C until needed (Gupta *et al.*, 2015). Metalloproteinase-8 level was detected by the Human MMP-8 ELISA Kit, depending on the colorimetric method as well. The kit has a sensitivity of 0.1 ng/mL, an optical density of 450 nm ± 2 nm, and a detection range of 0.16–10 ng/mL. By comparing the samples' optical densities with the standard curve, the MMP-8 concentration in the samples was determined.

Data Analysis

SPSS (version 30) was used to analyze the data. The data are displayed as mean ± standard deviation. The χ^2 test was used to assess categorical data. Two independent groups were compared using the Student's t-test. Pearson correlation was used to assess the degree of correlation between two quantitative variables. The statistical test was considered significant when the p-value was less than 0.05.

Results and Discussion

The mean age of the study participants is 45.19 ± 5.41 years. Of the 67 subjects included in the study, 31 were males versus 36 females, with a male to female ratio of 1:1.16. There was no statistically significant difference between patients with and without periodontitis in terms of age (P = 0.929), gender (P = 0.866), or body mass index (P = 0.205) **(Table 1)**.

Table 1. Demographic and body mass index comparison between the patients and controls.

Variable, Mean±SD	Cases (n=36)	Controls (n=31)	p value
Age, years	45.13 ± 5.84	45.25 ± 4.87	0.929
Sex:			
Male	17	14	0.866
Female	19	17	
Body mass index, kg/ m2	28.95 ± 7.25	27.50 ± 6.73	0.205

The biochemical characteristics of the patients and controls are compared **(Table 2)**. The mean of resistin (P value <0.001) and salivary metalloproteinase-8 (P value <0.001) was found to be statistically significant (higher) in the case group compared to the control group; however, the mean of vitamins A (P value <0.001), C (P value <0.001), D (P value <0.001), and E (P value <0.001) was statistically significant (lower).

Table 2. Comparing the biochemical variables of the patients and controls.

Variable, Mean±SD	Cases (n=36)	Controls (n=31)	p value
Resistin, ng/mL	8.33±0.95	5.97±0.80	<0.001
Vitamin A, ng/mL	587.95±15.08	604.10±11.79	<0.001
Vitamin C, µg/mL	5.39±0.71	9.15±0.65	<0.001
Vitamin D, ng/mL	18.53±4.44	26.06±8.02	<0.001
Vitamin E, µg/mL	16.24±3.51	21.90±3.73	<0.001
Salivary metalloproteinase-8, ng/ml	5.45±0.51	1.37±0.46	<0.001

The mean resistin levels were statistically significant (greater) in patients with normal levels of vitamin A, vitamin E, and salivary metalloproteinase-8 than in those with aberrant levels (P values < 0.001, 0.002, and < 0.001, respectively). Additionally, the mean resistin levels were shown to be statistically significant (lower) in patients with normal vitamin C and vitamin D levels compared to those with aberrant levels (P value < 0.001 and 0.027). Furthermore, there was no statistically significant difference in the mean resistin levels between the sexes (P value = 0.639). Finally, there was a statistically significant difference in the mean resistin levels between patients with a normal body mass index and those who were overweight or obese **(Table 3)**.

Table 3. Comparison between different variables regarding their mean of resistin levels.

	Variable	Resistin, ng/mL	p value
Sex	Male	7.33±1.36	0.638
	Female	7.15±1.55	
BMI	Normal	7.19±1.43	0.403

	Obesity	7.28±1.51	
Vitamin A level **(normal range 200-600 ng/mL)**	Normal	7.78±1.36	<0.001
	High	6.37±1.20	
Vitamin C level **(range 5-15 µg /mL)**	Normal	6.80±1.17	<0.001
	Low	9.46±0.55	
Vitamin D level **(range 30-100 ng/mL)**	Normal	6.34±0.50	0.027
	Deficient	6.91±1.25	
Vitamin E level **(range 5-20 µg /mL)**	Normal	7.07±1.13	0.002
	High	6.50±1.13	

The relationship between serum resistin and the other research factors is displayed in **Table 4**. The case and control groups had a significant, moderately negative correlation with vitamin A levels. But the case group showed a significantly strong negative correlation with vitamin C; and the control group showed a significant, moderate negative correlation with vitamin C.

Furthermore, the case and control groups had a significant, moderately positive correlation with salivary metalloproteinase-8. There was no significant correlation between serum resistin levels and patients' age, body mass index, vitamin D, and vitamin E among both case and control groups.

Table 4. Correlation between serum resistin and different variables included in the study.

Variable	Cases = 36		Controls = 31	
	Correlation coefficient	**p value**	**Correlation coefficient**	**p value**
Patient age	0.004	0.981	0.163	0.380
Body mass index	0.152	0.375	0.002	0.991
Vitamin A	-0.592	<0.001	-0.522	<0.001
Vitamin C	-0.855	<0.001	-0.614	<0.001
Vitamin D	-0.072	0.676	0.332	0.068
Vitamin E	0.053	0.758	0.241	0.191
Salivary metalloproteinase-8	0.371	0.025	0.490	0.005

According to **Figure 1**, periodontitis had an exceptional area under the curve (0.9803) at a resistin cutoff value of 6.8 (ng/mL), with a sensitivity of 87.5%, specificity of 96.4%, positive predictive value of 97.2%, negative predictive value of 87.1%, and test accuracy of 92.53%.
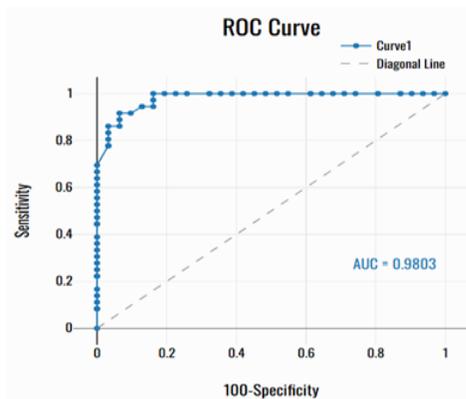

Figure 1. Resistin cutoff point for differentiation of periodontitis by using the Receiver Operating Characteristic curve.

Periodontal diseases are multifactorial infections caused by the interaction of a variety of bacteria with host cells and tissues, which results in the production of many cytokines and chemokines that induce the degeneration of periodontal structures.

Proinflammatory markers that play a significant role in the pathophysiology of periodontal illnesses can be used to measure the degree of inflammation in periodontal tissue. Additionally, gingival crevicular fluid is one of the least invasive diagnostic methods for determining the health state of periodontal tissue, including the degree of hard tissue degradation and the condition of the connective tissue (Majeed *et al.*, 2025).

The current study found that stage III periodontitis tended to affect both males and females without a significant difference; previous studies showed that males have a predominant prevalence of periodontitis in comparison to females (Shiau & Reynolds, 2010; Eke *et al.*, 2012; Ioannidou, 2017; Athul *et al.*, 2024). Anyhow, other studies showed females may have more severe periodontal symptoms during hormonal changes, such as, puberty and menopause (Jafri *et al.*, 2015; Boyapati *et al.*, 2021). This difference might be linked to factors like smoking habits, oral hygiene practices, the presence of chronic diseases, and hormonal influences. On the other hand, in spite of cases with stage III periodontitis having higher BMI than healthy controls, the difference was not significant. In contrast to Jia *et al.* and Çetin *et al.*, who found that overweight and obesity were significantly associated with severe periodontitis (stages III and IV) (Çetin *et al.*, 2022; Jia *et al.*, 2023). Anyhow, the observed difference is likely due to random variation and not a true effect due to different sample sizes.

This study found that the mean levels of resistin were significantly higher in patients with stage III periodontitis compared to healthy control subjects. This finding aligns with a study conducted in Baghdad (Al-Safi & Karam, 2015) and another study conducted in Malaysia (Md Tahir *et al*., 2020). The elevated resistin levels in periodontitis patients suggest a potential biomarker for the disease, helping in diagnosis and monitoring treatment response. Additionally, the current study found that patients with stage III periodontitis had significantly lower vitamin A levels than controls, which is consistent with several other studies (der Velden *et al*., 2011; Hans *et al*., 2023). The severity and course of periodontitis may be influenced by these lowered levels. Additionally, vitamin C levels were found to be significantly lower in patients with stage III periodontitis than in controls, which is in agreement with many studies (Chapple *et al*., 2018; Herrera *et al*., 2018; Kaźmierczak-Barańska *et al*., 2020; Hans *et al*., 2023). Vitamin C is an antioxidant and plays a crucial role in the synthesis of collagen, which is important for healthy gums and periodontal tissues. In the same way, the study found that vitamin D deficiency was also significantly lower in patients with stage III periodontitis compared to controls, which is consistent with other studies (Olszewska-Czyz & Firkova, 2022; Hans *et al*., 2023; Saleh *et al*., 2024). This may indicate that vitamin D is a contributing factor to the development and progression of periodontitis. It also highlights the potential benefit of assessing the state of vitamin D in periodontitis patients and considering supplementation as part of their treatment plan (Çınaroğlu *et al*., 2023; Fontaine *et al*., 2024; Karimov *et al*., 2024; Mori *et al*., 2024; Souza *et al*., 2024; Uneno *et al*., 2024; Coleman *et al*., 2025; Hussain *et al*., 2025; Ming *et al*., 2025; Ruiz *et al*., 2025). Additionally, the means of vitamin E levels were also found in this study to be lower in cases with stage III periodontitis than in controls, consistent with other studies (Shadisvaaran *et al*., 2021; Hans *et al*., 2023). This is due to the fact that vitamin E has an antioxidant effect that helps in the protection of the cell membranes from damage caused by reactive oxygen species produced by the body's inflammatory response to periodontitis. The mean of salivary metalloproteinase-8 found in the current study was significantly higher in cases with stage III periodontitis than in controls, which is parallel to other studies' findings (Kamil & Ali, 2023; Domokos *et al*., 2024). This elevated MMP-8 level is indicative of the increased tissue destruction occurring in the advanced stage of periodontal disease due to enzyme involvement in tissue breakdown.

This study found males had comparable resistin levels to females, while one study had found no significant difference in resistin levels between males and females (Chinonso *et al*., 2025), and another study had reported higher resistin levels in females compared to males (Al-ani *et al*., 2010). This might be due to the interaction of resistin levels and other factors, like obesity and insulin resistance leading to this complex variation across the population. Moreover, in this study, resistin level was found to be comparable between normal-weight and obese individuals, with no significant correlation between resistin and BMI, which agrees with one study (Heilbronn *et al*., 2004) and disagrees with another study (Gherlan *et al*., 2012). However, more research is needed to fully understand the role of resistin in correlation with obesity, particularly in different populations and under varying conditions.

Furthermore, the study discovered a significant moderate correlation between resistin and vitamin A in both groups; participants having normal vitamin A levels had higher resistin levels than those with high levels. This means that vitamin A was shown to inhibit resistin expression and it could regulate the inflammatory process, consistent findings obtained by other studies (Felipe *et al*., 2004; Corbetta *et al*., 2006). Additionally, the study found resistin levels were significantly higher in patients with low vitamin C levels, with a significantly strong negative correlation in the case group and a less negative (moderate) negative correlation with the control group between resistin and vitamin C. Other studies indicate that resistin levels are higher in individuals with low vitamin C levels (Bo *et al*., 2007). The exact mechanisms behind this negative correlation could be due to the antioxidant and anti-inflammatory properties of vitamin C, which might influence resistin production or release. This indicates that vitamin C supplementation with 1000 mg daily can result in a significant reduction of resistin levels. The same findings were also observed in the present study, with vitamin D: resistin being higher in the vitamin D-deficient group compared with patients with normal vitamin D, but there was no significant correlation between resistin and vitamin D, consistent with other studies (Vilarrasa *et al*., 2010; Geryk *et al*., 2024). Anyhow, other studies showed a significant negative correlation between resistin and vitamin D (Tariq *et al*., 2020). The inconsistent findings may be due to various factors, including differences in study populations (e.g., age, health status, and ethnicity), variations in vitamin D status assessment, and the complexity of the relationship between vitamin D, resistin, and other metabolic factors. Furthermore, this study found that resistin was significantly lower in patients with normal vitamin E levels in comparison to patients with high vitamin E levels, with no significant correlation between resistin and vitamin E. This means while the two groups had different resistin levels, the changes in vitamin E levels didn't consistently correspond with changes in resistin. This is consistent with other studies, which suggest that a daily intake of 400 IU of vitamin E may reduce resistin-related inflammatory and metabolic problems (Ghaffari, 2016). With regard to the correlation of resistin with salivary metalloproteinase-8 levels, the study found that resistin had a significant moderate positive correlation with salivary metalloproteinase-8 levels. Because metalloproteinase-8 is a proteinase that degrades collagen, a crucial part of the connective tissue in the gums and surrounding teeth, patients with periodontitis will ultimately have higher levels of metalloproteinase-8. It ultimately results in a rise in resistance. Similar conclusions were drawn from research conducted in Iraq (Al-Safi & Karam, 2015).

This study found the accuracy of resistin for the prediction of stage III periodontitis was 92.53%, with outstanding predictive power at an area under the curve of 0.9803. This means that resistin, a protein involved in inflammation, can be a useful biomarker for identifying individuals at risk of developing or having periodontitis. Unfortunately, no study has made such a finding to compare. But other studies found that a higher degree of accuracy in differentiating between individuals with and without periodontitis was obtained when combining multiple diagnostic criteria with resistin (Akram *et al*., 2017).

Conclusion

Resistin is an outstanding inflammatory mediator for the diagnosis of stage III periodontitis, as it showed a very high ability to predict patients with an advanced stage of periodontitis. Resistin exhibits a relatively positive link with salivary metalloproteinase-8 and a considerable, significant, strongly negative correlation with vitamin C and, to a lesser extent, with vitamin A. Resistin could play a key role in the diagnosis and treatment of many inflammatory and metabolic diseases.

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