Monaldi Archives for Chest Disease

eISSN 2532-5264 https://www.monaldi-archives.org/

Monaldi Arch Chest Dis 2026 [Online ahead of print]

To cite this Article:
Hirkane PS, Verma UP, Verma AK, et al. **Exploring the periodontal health status and level of matrix metalloproteinases in patients with interstitial lung disease: a case control study**. *Monaldi Arch Chest Dis* doi: 10.4081/monaldi.2026.3753

Submitted: 1-10-2025
Accepted: 1-07-2026

Exploring the periodontal health status and level of matrix metalloproteinases in patients with interstitial lung disease: a case control study

Prerna S. Hirkane,[1] Umesh Pratap Verma,[1] Ajay Kumar Verma,[2] Pavitra Rastogi,[1] Ashutosh Shrivastava,[3] Anjani Kumar Pathak[1]

[1]Department of Periodontology, Faculty of Dental Sciences, King George's Medical University, Lucknow, Uttar Pradesh; [2]Department of Respiratory Medicine, Dr Ram Manohar Lohiya Institute of Medical Sciences, Gomti Nagar, Lucknow, Uttar Pradesh; [3]Center for Advanced Research, King George's Medical University, Lucknow, Uttar Pradesh, India

Correspondence: Umesh Pratap Verma, Department of Periodontology, Faculty of Dental Sciences, King George's Medical University, Lucknow, Uttar Pradesh, India. Tel. : +919450195422. E-mail: umeshpratapverma@kgmcindia.edu

Contributions: Prerna S. Hirkane, Umesh Pratap Verma, Ajay Kumar Verma, Pavitra Rastogi: concept, literature search. Prerna S. Hirkane, Umesh Pratap Verma, Ajay Kumar Verma, Ashutosh Shrivastava: design. Prerna S. Hirkane, Umesh Pratap Verma, Ajay Kumar Verma, Pavitra Rastogi, Anjani Kumar Pathak: definition of intellectual content, data acquisition. Prerna S. Hirkane, Umesh Pratap Verma, Ashutosh Shrivastava, Anjani Kumar Pathak: data analysis. Prerna S. Hirkane: manuscript editing. All authors: manuscript preparation, manuscript review.

Conflict of interest: the authors declare that they have no conflict of interest regardingthe publication of this paper.

Ethics approval and consent to participate: this study was approved by the Institutional Ethics Committee of King George's Medical University, U.P, Lucknow, India (Ref. code: XI-PGTSC-IIA/P15).

Informed consent: written informed consent was obtained from all participants prior to enrolment in the study.

Patient consent for publication: written informed consent was obtained from a legally authorized representative for anonymized patient information to be published in this article. The manuscript does not contain any individual person's data in any form

Availability of data and materials: the datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Acknowledgments: the authors extend their gratitude to all patients involved in the study. They also sincerely acknowledge Dr. Ipshita Potlia for her patience and constant support with the statistical analysis. We would also like to thank Miss. Shiva Shukla for her assistance during the laboratory procedures.

Declaration of generative artificial intelligence and artificial intelligence-assisted technologies in the writing process: the authors declare that no generative artificial intelligence (AI) or AI-assisted technologies were used in the writing, editing, or preparation of this manuscript.

Abstract

Periodontitis has been linked to several respiratory diseases such as chronic obstructive pulmonary disease, asthma, and lung cancer; however, the role of periodontal health status and matrix metalloproteinases (MMPs) in interstitial lung diseases (ILDs) remains largely unexplored. The present study aimed to investigate periodontal health and evaluate serum and salivary levels of MMP-7, MMP-8, and tissue inhibitor of metalloproteinase-1 (TIMP-1) in patients with ILDs. A total of 75 individuals were included and divided equally into three groups: healthy controls, patients with chronic periodontitis, and patients with ILDs. Demographic factors such as age, gender, and socioeconomic status were recorded, along with clinical parameters including plaque index, gingival index, probing pocket depth, and clinical attachment level. The findings revealed that levels of MMP-7 and MMP-8 were significantly elevated in both the periodontitis and ILD groups compared to healthy controls, while TIMP-1 did not show notable variation among groups. Clinical periodontal parameters were also higher in patients with ILDs as well as those with chronic periodontitis. These results suggest a possible link between ILD and chronic periodontitis, both from clinical and biochemical perspectives. The study provides pioneering evidence in the emerging field of oral-systemic research, emphasizing the need for further investigations with larger sample sizes and interventional designs to strengthen the evidence base and explore possible genetic associations underlying this relationship.

Key words: interstitial lung diseases, respiratory diseases, perio-systemic, MMPs, TIMP.

Introduction

Interstitial lung disease (ILD) is an umbrella term that encompasses a heterogeneous group of lung diseases characterized by the presence of non-infective infiltrates, predominantly involving the pulmonary interstitium and alveoli. Sarcoidosis and Idiopathic Pulmonary Fibrosis (IPF) have emerged as the predominant ILDs across North America and Europe, whereas hypersensitivity pneumonitis has shown higher prevalence rates in Asia, particularly in India (10.7%–47.3%) and Pakistan (12.6%) [1].

Research has increasingly supported the possibility that periodontal diseases may influence certain systemic conditions such as cardiovascular diseases, diabetes mellitus, and various respiratory ailments. In addition, studies have demonstrated an association between chronic periodontitis and reduced respiratory function, with systemic inflammation providing a possible biological explanation for this relationship.

Periodontal diseases comprise a broad group of inflammatory disorders affecting the gingiva, alveolar bone, and periodontal ligament, which support the teeth. These conditions may lead to tooth loss and contribute to systemic inflammation. Chronic periodontitis primarily affects adults. In a Korean national survey involving 5,878 adults, a significantly higher prevalence of periodontitis was observed among individuals with Chronic Obstructive Pulmonary Disease (COPD) compared to those without COPD, indicating a possible association between the two disease conditions [2].

According to a 2019 systematic review and meta-analysis, respiratory health disparities are greater and respiratory function is poorer among children, adolescents, and young adults from disadvantaged socioeconomic backgrounds [3].

The use of saliva for biomarker analysis offers a non-invasive approach and enables continuous monitoring of disease progression and therapeutic response. In addition, serum biomarkers have gained attention as potential indicators for both periodontal and respiratory diseases. Similarly, in respiratory diseases such as asthma, COPD, and ILD, biomarkers including various cytokines and matrix metalloproteinases (MMPs) have been investigated for their association with disease severity and exacerbations [4].

Considering the limited availability of literature regarding the interrelationship between periodontal health and interstitial lung disease, the present case-control study was undertaken to evaluate the association between chronic periodontitis and interstitial lung diseases through clinical and biochemical parameters.

Materials and Methods

Study design

The present case-control study was carried out in the Department of Periodontology, Faculty of Dental Sciences, King George's Medical University, U.P, Lucknow in collaboration with Department of Respiratory Medicine and Centre for advance research. Institutional ethical committee permission and written patient consent was taken prior to the beginning of the study (Ref. code: XI-PGTSC-IIA/P15).

The inclusion criteria encompassed previously untreated adults aged 25 to 60, with generalized chronic periodontitis according to the American Academy of Periodontology (AAP 1999) criteria. Additionally, dentulous patients with >20 teeth, probing pocket depth (PPD) ≥ 5mm, clinical attachment level (CAL) ≥ 4mm were included. Patients with confirmed interstitial lung diseases, including Idiopathic Pulmonary Fibrosis (IPF), based on clinical, radiological, and/or pulmonary function test findings, were included in the study. Patients with ILD were receiving antifibrotic therapy, including Nintedanib and Pirfenidone, as part of their medical management. Exclusion criteria comprised completely edentulous individuals, those with medication or systemic diseases affecting periodontal health, lactating or pregnant women, and patients unwilling to give consent.

Clinical examination

All clinical parameters gingival index (GI), plaque index(PI), probing pocket depth (PPD), clinical attachment level (CAL) were recorded at all the 6 sites with a graduated periodontal probe (University of North Carolina {UNC-15}, Hu-Freidy, Chicago, IL, USA). All the clinical parameters were recorded in specialised proforma (Case-sheet).

Study groups

All clinical parameters were measured in subjects satisfying the inclusion criteria and assigned into the following 3 groups.

Group I: Healthy subjects (without chronic periodontitis and interstitial lung disease)

Group II: Subjects having Chronic Periodontitis

Group III: Subjects having Interstitial Lung Diseases (ILD)- Idiopathic Pulmonary fibrosis.

Sample collection

Subjects were scheduled for appointments in the morning, 2-3 hours after breakfast, and were comfortably seated in the dental chair. Whole saliva samples were collected by having patients expectorate into pre-labelled Eppendorf tubes. Additionally, 3 ml of peripheral venous blood samples were obtained from each patient using the standard venipuncture method and collected in vacutainer tubes. These blood samples were then centrifuged at a speed of 3000 rpm for 10 minutes. Both saliva and serum samples were promptly stored at -80°C until the assay, aiming to minimize the loss of reactivity of biomarkers.

Biochemical analysis

Determination of MMP-7, MMP-8 and TIMP-1 in saliva and serum

The ELISA kit* (MMP-7 catalog No. E-EL-H1449, MMP-8 catalog No. E-EL-H1450, TIMP-1 catalog No. E-EL-H0184) used the Sandwich-ELISA principle. Samples or standards are added to the plate wells, where they bind to the respective antibodies. Subsequently, a biotinylated detection antibody specific for matrix metalloproteinase-7 (MMP-7), matrix metalloproteinase-8 (MMP-8), and tissue inhibitor of metalloproteinases-1 (TIMP-1), along with Horseradish Peroxidase (HRP) conjugate, are added sequentially and incubated. Unbound components are washed away, and a substrate solution is added, causing wells containing MMP-7, MMP-8, and TIMP-1 biotinylated detection antibodies and HRP conjugate to turn blue. The enzyme-substrate reaction is halted by the addition of a stop solution, resulting in a color change to yellow. Optical density (OD) is measured at 450 nm, with a detection range of 0.16-10 ng/mL. The OD value correlates with the concentration of MMP-7, MMP-8, and TIMP-1.

Statistical analysis

Statistical analyses were performed using the SPSS 26 statistical software program (SPSS Inc.). The p value was set at 0.05 to be significant, and p value less than 0.01 was considered as highly significant. Power of the study was fixed at 80% and confidence level was set at 95%.

Results

A total of 75 subjects were included in the study and were divided into three groups. Group 1 (n=25) consisted of healthy subjects with a mean age of 31.68 years, whereas Group 2 (n=25) and Group 3 (n=25) included subjects with chronic periodontitis and interstitial lung diseases, with mean ages of 47.8 years and 47.16 years, respectively. A higher proportion of males was observed in the chronic periodontitis group (15 males and 10 females), while females were predominant in the healthy and ILD groups (Table 1).

No significant differences were observed in clinical periodontal parameters, including GI, PI, PPD, and CAL, between the chronic periodontitis and ILD groups. However, significant differences were observed when healthy subjects were compared with subjects having chronic periodontitis and ILD (Table 2).

Table 3 compares the salivary and serum levels of MMP-7, MMP-8, and TIMP-1 among the three groups. Salivary and serum MMP-7 and MMP-8 levels were found to be elevated in both the chronic periodontitis and ILD groups compared to healthy subjects. However, only negligible differences were observed between the chronic periodontitis and ILD groups. In addition, no statistically significant difference was observed in salivary and serum TIMP-1 levels among the three groups.

Figures 1 and 2 illustrate the salivary and serum levels of MMP-7, MMP-8, and TIMP-1 among the study groups.

Discussion

The present case-control study evaluated the association between chronic periodontitis (CP) and interstitial lung diseases (ILD) using clinical periodontal parameters and salivary and serum biomarkers, including MMP-7, MMP-8, and TIMP-1. The findings demonstrated that periodontal clinical parameters, along with salivary and serum MMP-7 and MMP-8 levels, were elevated in both CP and ILD groups compared to healthy controls. However, TIMP-1 levels did not show significant differences among the groups.

In our study, the mean age of subjects in the CP and ILD groups was higher compared to healthy controls. Both chronic periodontitis and ILD are more commonly associated with advancing age. Previous studies have shown that Idiopathic Pulmonary Fibrosis (IPF) is more prevalent among older individuals, while the severity and prevalence of

chronic periodontitis also increase with age. Gender distribution in the present study showed male predominance in the CP group, whereas females were more prevalent in the ILD group. These findings may be attributed to the higher prevalence of connective tissue disease-associated ILDs among females.

The majority of patients with CP and ILD belonged to lower socioeconomic backgrounds according to the Kuppuswamy socioeconomic scale 2022 [5]. Lower socioeconomic status has been associated with poor oral hygiene, limited healthcare access, and worse respiratory outcomes. Previous studies have also reported an increased prevalence of ILD and periodontal disease among individuals from lower socioeconomic groups.

Clinical periodontal parameters including PI, GI, PPD, and CAL were significantly higher in CP and ILD groups compared to healthy subjects. Poor oral hygiene and increased microbial biofilm accumulation may contribute to both periodontal inflammation and respiratory disease progression. Several mechanisms have been proposed linking oral pathogens with respiratory diseases, including aspiration of periodontal pathogens into the lungs, alteration of respiratory epithelium by inflammatory cytokines, and modification of mucosal surfaces by bacterial enzymes [6].

Han MK et al. (2014) demonstrated an association between Streptococcus and Staphylococcus species and progression of idiopathic pulmonary fibrosis (IPF) [7]. Other studies have reported the presence of Prevotella, Fusobacterium, and Porphyromonas gingivalis in both chronic periodontitis and respiratory diseases [8,9]. These findings suggest a possible microbial and inflammatory link between CP and ILD.

A significant difference in gingival index and probing pocket depth was observed in ILD and CP groups compared to healthy controls. Increased periodontal inflammation may be associated with elevated systemic inflammatory burden. Studies have demonstrated associations between bleeding on probing and IPF severity [10]. In addition, periodontal pathogens such as Porphyromonas gingivalis induces pro-inflammatory cytokines like IL-6 and IL-8 in respiratory epithelial cells via toll-like receptor 2 (TLR-2), exacerbating inflammation and stimulating extracellular matrix production. Furthermore, heightened expression of TLR2 and TLR4 in the lungs, as observed in patients with interstitial lung diseases (ILD), suggests a potential role in ILD pathogenesis. These findings underscore a possible link between periodontal pathogens and respiratory conditions [11,12].

Intergroup analysis revealed a significant difference ($p<0.001$), with the highest mean clinical attachment loss (CAL) observed in CP patients. A longitudinal study also reported a higher incidence of respiratory disease-related mortality among individuals with periodontal pockets deeper than 4 mm and the presence of at least 10 teeth [13]. Since PI, GI, PPD, and CAL are important clinical indicators of chronic periodontal inflammation, these findings suggest that periodontal disease and respiratory diseases may share common inflammatory pathways. Furthermore, the indirect mechanisms, such as low-grade inflammation and cytokine impact, further emphasize the intricate relationship between the two conditions [14].

Biomarker analysis revealed significantly increased salivary and serum MMP-7 and MMP-8 levels in CP and ILD groups (Figures 1 and 2). MMPs are known to participate in tissue destruction, extracellular matrix remodeling, and inflammatory responses. They may be detected in various bodily fluids and tissues such as gingival crevicular fluid (GCF), peripheral blood, airway, saliva and lung parenchyma. Prashanthi (2022)reported significantly higher salivary MMP-7 levels in periodontitis patients compared to healthy controls [15]. Similarly, increased MMP-7 expression has been observed in interstitial lung disease (ILD) patients. In chronic periodontitis, serum MMP-7 levels have also been reported to be elevated in some studies, although other reports have found comparable levels between periodontitis and healthy individuals [16].

A similar trend was observed for MMP-8 levels in both saliva and serum across the groups (Group 1 < Group 2 < Group 3), as shown in Table 3 and Figures 1 and 2. Elevated salivary MMP-8 has been reported in chronic periodontitis, while increased serum levels have been observed in ILD and are linked to fibrocyte activity and disease progression, particularly in IPF [17,18].

In contrast, TIMP-1 levels did not differ significantly among the groups. Similar observations have been reported in previous studies, where TIMP-1 levels remained relatively stable despite inflammatory disease progression [19,20].

Although direct evidence linking chronic periodontitis and interstitial lung diseases remains limited, the present findings suggest a possible association through shared inflammatory responses, microbial burden, and biomarker expression. Further longitudinal and multicentric studies with larger sample sizes are required to better understand the direct or indirect relationship between periodontal disease and ILD.

Conclusions

In our study, interstitial lung diseases and chronic periodontitis demonstrated shared clinical characteristics and similar biochemical profiles. Patients with these conditions exhibited distinct periodontal health markers compared to healthy individuals, with elevated MMP-7 and MMP-8 levels observed in both groups, suggesting their potential role as common inflammatory biomarkers. Further studies with larger sample sizes are needed to validate these findings and explore underlying mechanisms. Diagnostic kits based on these markers could enhance treatment planning and improve the quality of life for affected individuals.

References

1. Singh S, Collins BF, Sharma BB, et al. Interstitial lung disease in India. Results of a prospective registry. Am J Respir Crit Care Med 2017;195:801-13.
2. Chung JH, Hwang HJ, Kim SH, et al. Associations between periodontitis and chronic obstructive pulmonary disease: the 2010 to 2012 Korean National Health and Nutrition Examination Survey. J Periodontol 2016;87:864-71.
3. Rocha V, Soares S, Stringhini S, et al. Socioeconomic circumstances and respiratory function from childhood to early adulthood: a systematic review and meta-analysis. BMJ Open 2019;9:e027528.
4. Hirkane PS, Verma UP, Verma AK, et al. Exploring the relation between interstitial lung diseases and chronic periodontitis: a systematic review. Cureus 2024;16:e53157.
5. Sood P, Bindra S. Modified Kuppuswamy socioeconomic scale: 2022 update of India. Int J Community Med Public Health 2022;9:3841.
6. Loesche WJ. Microbiology of dental decay and periodontal disease. In: Baron S, ed. Medical microbiology. 4th ed. Galveston, TX, USA: University of Texas Medical Branch at Galveston; 1996.
7. Han MK, Zhou Y, Murray S, et al. Lung microbiome and disease progression in idiopathic pulmonary fibrosis: an analysis of the COMET study. Lancet Respir Med 2014;2:548-56.
8. Huang Y, Ma SF, Espindola MS, et al. Microbes are associated with host innate immune response in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med

2017;196:208-19.
9. Mombelli A. Microbial colonization of the periodontal pocket and its significance for periodontal therapy. Periodontol 2000 2018;76:85-96.
10. Barczyk A, Białas A, Piotrowski W, et al. Oral health and wellbeing of patients with idiopathic pulmonary fibrosis. J Health Study Med 2023;5-19.
11. Shi T, Wang J, Dong J, et al. Periodontopathogens porphyromonas gingivalis and fusobacterium nucleatum and their roles in the progression of respiratory siseases. Pathogens 2023;12:1110.
12. Watanabe N, Yokoe S, Ogata Y, et al. Exposure to porphyromonas gingivalis induces production of proinflammatory cytokine via TLR2 from human respiratory epithelial cells. J Clin Med 2020;9:3433.
13. Awano S, Ansai T, Takata Y, et al. Oral health and mortality risk from pneumonia in the elderly. J Dent Res 2008;87:334-9.
14. Herrera D, Sanz M, Shapira L, et al. Association between periodontal diseases and cardiovascular diseases, diabetes and respiratory diseases: consensus report of the Joint Workshop by the European Federation of Periodontology (EFP) and the European arm of the World Organization of Family Doctors (WONCA Europe). J Clin Periodontol 2023;50:819-41.
15. Prashanthi S. Evaluation of salivary levels of matrix metalloproteinase 7 (MMP 7) in healthy and periodontitis patients: a cross sectional study. Tiruchengode, India: KSR Institute of Dental Science and Research; 2022.
16. Bauer Y, White ES, de Bernard S, et al. MMP-7 is a predictive biomarker of disease progression in patients with idiopathic pulmonary fibrosis. ERJ Open Res 2017;3:00074-2016.
17. Morais A, Beltrão M, Sokhatska O, et al. Serum metalloproteinases 1 and 7 in the diagnosis of idiopathic pulmonary fibrosis and other interstitial pneumonias. Respir Med 2015;109:1063-8.
18. Gursoy UK, Könönen E, Huumonen S, et al. Salivary type I collagen degradation end-products and related matrix metalloproteinases in periodontitis. J Clin Periodontol 2013;40:18-25.
19. Craig VJ, Polverino F, Laucho-Contreras ME, et al. Mononuclear phagocytes and airway epithelial cells: novel sources of matrix metalloproteinase-8 (MMP-8) in

patients with idiopathic pulmonary fibrosis. PLoS One 2014;9:e97485.

20. Hernández Ríos M, Sorsa T, Obregón F, et al. Proteolytic roles of matrix metalloproteinase (MMP)-13 during progression of chronic periodontitis: initial evidence for MMP-13/MMP-9 activation cascade. J Clin Periodontol 2009;36:1011-7.

Table 1. Demographic data.

	GROUP 1	GROUP 2	GROUP 3
AGE	31.68	47.8	47.16
GENDER DISTRIBUTION			
MALE	11	15	11
FEMALE	14	10	14
*SOCIO-ECONOMIC STATUS		KUPPUSWAMY	SES 2022
*UPPER MIDDLE (II)	36%	16%	0
*LOWER MIDDLE (III)	40%	32%	32%
*UPPER LOWER (IV)	24%	44%	48%
*LOWER (V)	0	8%	20%

*SES score-Upper middle (II): 16-25, Lower middle (III): 11-15, Upper lower (IV): 5-10, Lower (V):<5, Upper (I) : 26-29.

Table 2. Clinical parameters.

	Group 1	Group 2	Group 3	Group 1 *vs.* 2	Group 1 *vs.* 3	Group 2 *vs.* 3
GI	1.27±0.17	2.58±0.29	2-67±0.25	p<0.001	p<0.001	p=0.19
PI	1.35±0.27	2.51±0.32	2.44±0.41	p<0.001	p<0.001	p=0.65
PPD	2.22±0.49	4.59±0.66	4.23±0.49	p<0.001	p<0.001	p =0.06
CAL	2.22±0.49	4.77±0.62	4.36±0.51	p<0.001	p<0.001	p = 0.02

p<0.01 is statistically significant; *p<0.05 is statistically significant; NS, not significant.

Table 3. Biochemical analysis of saliva and serum MMP and TIMP-1.

	Group 1	Group 2	Group 3	Group 1 *vs.* 2	Group 1 *vs.* 3	Group 2 *vs.* 3
Salivary MMP-7 level	5.12±2.4	7.68±2.6	7.97±2.5	p<0.001	p<0.001	p=0.91
Salivary MMP-8 level	6.99±3.4	10.06±0.9	10.15±0.63	p<0.001	p<0.001	p=0.98
Salivary TIMP-1 level	5.46±3.3	4.84±1.85	5.35±2.60	p=0.69	p=0.69 (NS)	p=0.69 (NS)
Serum MMP-7 level	4.36±3.4	7.84±2.2	6.54±2.28	p<0.001	p<0.001	p=0.26 (NS)
Serum MMP-8 level	7.47±2.6	10.08±1.64	10.72±0.17	p<0.001	p<0.001	p=0.42 (NS)
Serum TIMP-1 level	6.8±2.5	5.84±2.4	5.26±2.0	p=0.074 (NS)	p=0.074 (NS)	p=0.074 (NS)

p<0.01 is statistically significant; *p<0.05 is statistically significant; NS, not significant.

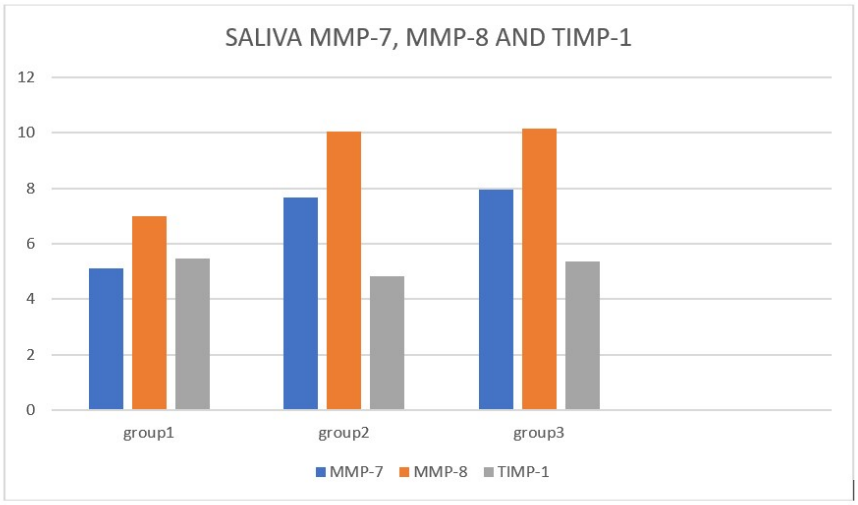

Figure 1. Saliva MMP-7, MMP-8 and TIMP-1 levels.

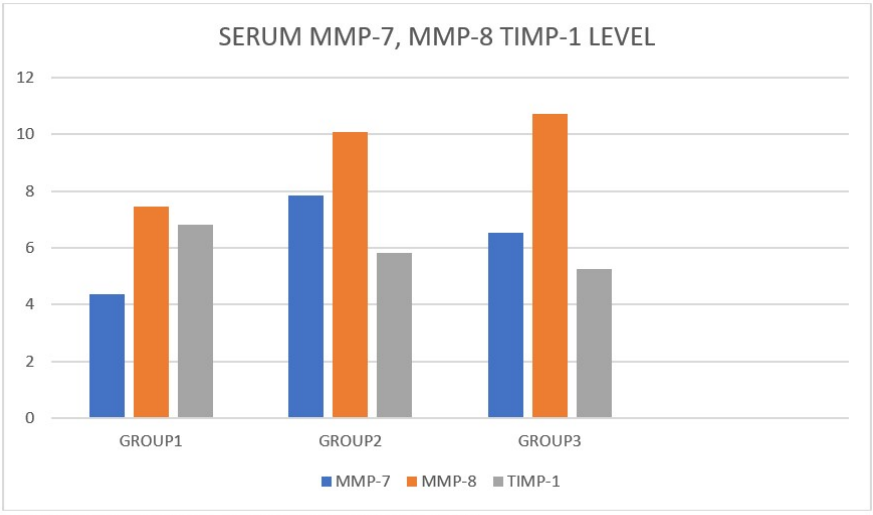

Figure 2. Serum MMP-7, MMP-8 and TIMP-1 level.