Journal of Dentomaxillofacial Radiology, Pathology and Surgery

Winter 2023. Volume 12. Number 1

ReviewPaper: Effect of Periodontal Treatment on the Negative Acute Phase Proteins in Patients with Periodontitis

Ashkan Salari[1*], Vanousheh Norouzi[2]

[1] Assistant Professor, Dental Sciences Research Center, Department of Periodontics, School of Dentistry, Guilan University of Medical Sciences, Rasht, Iran
[2] Postgraduate of Student, Department of Periodontics, School of Dentistry, Guilan University of Medical Sciences, Rasht, Iran

Use your device to scan and read the article online

Citation Salari A, Norouzi V. Effect of Periodontal Treatment on the Negative Acute Phase Proteins in Patients with Periodontitis. Journal of Dentomaxillofacial Radiology, Pathology and Surgery. 2023; 12(1):36-40.

http://dx.doi.org/10.32592/3dj.12.1.36

Article info:
Received: 11 Apr 2023
Accepted: 12 Jun 2023
Available Online: 27 Jun 2023

Keywords:
Acute phase proteins
Inflammatory mediators
Periodontal debridement
Periodontitis

ABSTRACT

Periodontitis is an inflammatory-infectious disease of tooth-supporting structures that results in the progressive destruction of the periodontal ligament and alveolar bone due to an imbalance between the host defense and microorganisms. Subgingival microbiota has a significant role in the initiation and progression of periodontitis, affecting the innate and acquired immune responses by the infiltration of immune cells such as monocytes and polymorphonuclear cells that are abundant under inflammatory conditions. The immune cells induce the release of proinflammatory cytokines that lead to the destruction of periodontal connective tissue and the alveolar bone. Cytokines activate hepatocytes to produce acute phase proteins as a component of the nonspecific response. These proteins are a group of proteins that increase (positive type) and decrease (negative type) under inflammatory conditions. This response is called the acute phase response (APR) that occurs after the initiation of a systemic inflammatory reaction. Nonsurgical periodontal therapy is the first stage of treatment for periodontitis. Its aim is to eliminate etiologic agents and decrease inflammation. The aim of this review article was to evaluate the effect of periodontitis as an inflammatory condition and its treatment on the concentrations of negative acute phase proteins.

**** Corresponding Authors:***
Ashkan Salari.
Address: *Dental Sciences Research Center, Department of Periodontics, School of Dentistry, Guilan University of Medical Sciences, Rasht, Iran.*
Tel: *+981333330862*
E-mail: *drashkan_salary@yahoo.com*

1. Introduction

Periodontitis is an inflammatory disease of tooth-supporting structures caused by some specific microorganisms, resulting in the progressive destruction of the tissues surrounding the teeth, such as the periodontal ligament and alveolar bone (1). In this disease, gram-negative bacteria in the subgingival plaque produce endotoxins that interact with the toll-like receptors on the surface of polymorphonuclear (leukocytes and monocytes). Such interaction affects the innate and acquired immune responses, finally leading to the release of proinflammatory cytokines that activate the local and systemic inflammatory responses. These proinflammatory cytokines that originate from the diseased site activate the hepatocytes to produce acute phase proteins as a component of the nonspecific response (2). In patients with periodontitis, there is an increase in proinflammatory cytokines such as IL-1β, IL-6, and TNF-α that decrease some acute phase proteins in the plasma, such as serum albumin. This effect is the opposite of the positive acute phase proteins such as C-reactive protein (3-9). The acute phase response induced by microorganisms leads to homeostasis and elimination of the factor causing the imbalance, with systemic effects (5,10,11).

The first step in treating periodontitis is the nonsurgical periodontal treatment to eliminate etiologic factors, finally resulting in a change in the level of proinflammatory markers such as acute phase proteins. The clinical outcome of nonsurgical periodontal treatment is a decrease in gingival inflammation, a decrease in pocket depths, and a decrease in clinical attachment levels (1).

Acute phase proteins are a group of proteins whose concentrations increase in response to inflammatory conditions (such as periodontal disease) (the positive type), with a decrease in the concentrations of some others (the negative type) (2). In addition, they indicate the presence, severity, and timeline of inflammation because they are released into the bloodstream at high levels under inflammatory conditions and in response to injuries or infections and can be used for routine evaluation of inflammatory conditions (12). They are considered a component of the innate immune system that minimize tissue injuries and increase reconstruction and regenerative homeostasis (Figure 1) (13).

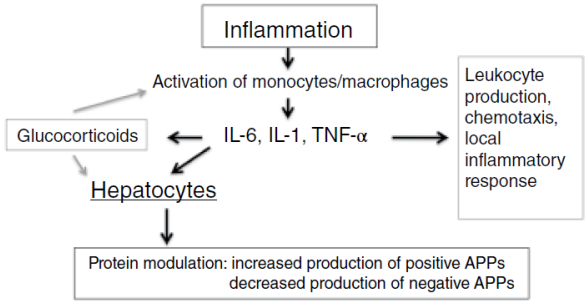

Figure 1. Schematic representation of the acute phase response

Acute phase proteins undergo changes in their concentrations up to 25% under inflammatory conditions, including the complement proteins, transport proteins, antiproteases, and different inflammatory mediators. The response these proteins mount in response to inflammatory conditions is called the acute phase response (APR), which occurs almost 90 minutes after the initiation of a systemic inflammatory reaction (2). When a tissue injury occurs, inflammatory mediators (such as cytokines) increase. These cytokines stimulate different cells, resulting in acute phase response, finally increasing the production of acute phase proteins by the liver. Some studies have shown that extrahepatic tissues, too, can produce these proteins (13).

The present review aims to evaluate studies on negative acute phase proteins and the effect of periodontitis and periodontal treatment on these proteins.

2. Discussion

Acute phase proteins are divided into two groups: positive and negative. They differ in their extent of change under inflammatory conditions; the negative ones decrease in response to inflammatory conditions. Therefore, it is expected that they will increase after the resolution of the inflammatory process (Table 1) (2).

Table 1. The negative acute phase proteins

Negative acute phase proteins
Albumin
Transferrin
Retinol-binding protein (RBP)
Fetuin-A
S100A12

The negative acute phase proteins have a function opposite to that of the positive proteins under inflammatory conditions, including increasing coagulation, increasing serum levels of free cortisol, and homeostasis after stress (2).

Albumin is a negative acute phase protein whose serum levels can be used to determine the general health status. Malnutrition and inflammation can decrease the serum levels of this protein by decreasing its production rate. Chronic inflammatory disease and other inflammatory conditions can lead to the release of inflammatory cytokines such as IL-1, IL-6, and TNF-α, finally decreasing the serum albumin levels (14).

Kaur et al and Kolte et al reported an inverse relationship between serum albumin levels and chronic periodontitis, i.e., this disease leads to a decrease in serum albumin levels and an increase in the loss of clinical attachments. Therefore, albumin can be used as an inflammatory marker to monitor the severity of periodontal disease (9,14).

Lalkota et al reported a significant relationship between increased serum levels of alkaline phosphate and decreased serum levels of albumin in smoking patients with periodontitis compared to nonsmoking patients with periodontitis (15).

Pydi et al evaluated and compared the albumin serum levels between healthy individuals and patients with gingivitis and periodontitis and reported an inverse relationship between the gingival index score and albumin serum levels; i.e., there was a significant decrease in albumin serum levels and an increase in the gingival index score and increased loss of clinical attachments (16).

Shirmohammadi et al reported lower albumin serum levels in patients with chronic periodontitis compared to healthy individuals, which increased significantly three months after nonsurgical periodontal treatment (17).

Ashtankar et al reported a significant increase in albumin serum levels three months after periodontal surgery, concluding that open flap debridement surgical treatment had a positive effect on the serum levels of albumin (18).

Another negative acute phase protein is a glycoprotein called transferrin, whose serum levels decrease during inflammation. It has general functions, including transferring serum iron to body organs, a destructive effect on bacteria, and a role in innate immunity. Wu et al evaluated decreased hemoglobin levels and iron metabolic disorders in a systematic review and meta-analysis in patients with chronic periodontitis and reported decreased transferrin levels (19). Costa et al reported that the transferrin levels were correlated with areas where the clinical attachment loss was ≥4 mm .(20) Shirmohammadi et al reported an inverse relationship between the transferrin serum levels and generalized chronic periodontitis; increased transferrin serum levels were observed three months after nonsurgical periodontal treatment (21).

Vitamin A circulates in the bloodstream in the form of retinol. Retinol-binding protein comprises 182 amino acids and has a key role in vision (22). In addition, it has an important role in maintaining epithelial function. Recently synthesized RBP achieves a retinol molecule in the endoplasmic reticulum of hepatocytes and then is secreted into the plasma, where it is combined with the thyroxin-binding prealbumin. Retinol has an important role in the growth and differentiation of different body tissues (23). Martinez-Herrera et al reported high serum levels of RBP4 in patients with chronic periodontitis, which decreased three months after nonsurgical periodontal treatment (24).

Fetuin-A is a glycoprotein secreted by the liver, which has been isolated from the bovine fetal serum. Some recent studies have shown a relationship between fetuin-A and systemic diseases and its several pathologic functions. S100A12 is a calcium-binding protein from the S100 proteins subfamily related to myeloid, which serves as an alarmin to induce innate proinflammatory immune responses. It is related to several chronic inflammatory diseases. However, its role in the immunopathology of periodontitis is unknown to a great extent (22,25).

Türer et al reported a negative relationship between the increased severity of periodontal disease and the serum levels of fetuin-A (25). Lira-Junior et al reported that in patients with stage III and IV periodontitis, the serum levels of S100A12 were significantly higher than those without the disease. In addition, there was a relationship between the salivary levels of S100A12 and the inflammatory grade of the gingiva and the presence of pathologic periodontal pockets (22).

Furugen et al showed significantly lower serum fetuin-A levels in patients with moderate to severe chronic periodontitis than in patients with mild chronic periodontitis or healthy individuals. There was a negative relationship between the clinical attachment loss and serum levels of fetuin-A. The worse periodontal status was related to lower serum levels of fetuin-A. It was concluded that fetuin-A could be used as a marker for chronic periodontitis (26).

Ersin Kalkan et al reported significantly higher salivary levels of fetuin-A and S100A12 in patients with

chronic periodontitis than in the control group, which increased to levels above the baseline after nonsurgical periodontal treatment. Therefore, it was concluded that there was a positive relationship between fetuin-A and S100A12 levels at baseline, and an increase in the severity of periodontal disease decreased the salivary levels of fetuin-A and S100A12 (27).

Lobao et al reported that in chronic periodontitis, the serum levels of fetuin-A decreased, and the serum levels of MMP-7 increased. Three months after nonsurgical periodontal treatment, there was a significant increase in the serum levels of fetuin-A and a significant decrease in the serum levels of MMP-7 (12).

Nejadi et al evaluated the effect of nonsurgical periodontal treatment on gingival crevicular fluid levels of S100A12 and IL-22 and concluded that there was a negative relationship between S100A12 concentration and the probing depth before treatment. One month after nonsurgical periodontal treatment, there was a significant relationship between a decrease in pocket depths and the loss of clinical attachments and an increase in the concentration of S100A12 in the gingival crevicular fluid. Therefore, it might be concluded that S100A12 has a protective role in chronic periodontitis and the success of phase I periodontal treatment (28).

3. Conclusion

It can be concluded from the present review study that periodontitis, as an inflammatory disease, can lead to changes in the levels of negative acute phase proteins, with decreases in the levels of these proteins that increase after surgical and nonsurgical periodontal treatment. However, it should be pointed out that proteins recognized to date as negative acute phase proteins are less numerous than positive ones, and more such proteins might be identified in the future.

Ethical Considerations

Compliance with ethical guidelines

Not applicable.

Funding

None.

Authors'contributions

AS initiated, conceptualized, and supervised the review work. VN performed data collection. AS and VN wrote the manuscript. All authors read and approved the final manuscript.

Conflict of Interests

The authors declare no conflict of interest.

Availability of data and material

The data used to support the findings of this study are available from the corresponding author upon request.

Acknowledgments

None.

References

1. Gupta S, Gupta I, Gupta R, Amaranath B J, Goswami A, Singh D. A Comparative evaluation of serum CRP levels in Chronic and aggressive periodontitis patients before and after non-surgical periodontal therapy-a clinical study. Uni J Dent Sci. 2021; 6(3): 09-15. [DOI: 10.21276/ujds.2020.6.3.2]
2. Polepalle T, Moogala S, Boggarapu S, Pesala DS, Palagi FB. Acute Phase Proteins and Their Role in Periodontitis: A Review. J Clin Diagn Res. 2015;9(11):ZE01-5. [DOI: 10.7860/JCDR/2015/15692.6728] [PMID] [PMCID]
3. Górska R, Gregorek H, Kowalski J, Laskus-Perendyk A, Syczewska M, Madaliński K. Relationship between clinical parameters and cytokine profiles in inflamed gingival tissue and serum samples from patients with chronic periodontitis. J Clin Periodontol. 2003;30(12):1046-52. [DOI: 10.1046/j.0303-6979.2003.00425.x]
4. Craig RG, Yip JK, So MK, Boylan RJ, Socransky SS, Haffajee AD. Relationship of destructive periodontal disease to the acute-phase response. J Periodontol. 2003;74(7):1007-16. [DOI: 10.1902/jop.2003.74.7.1007]
5. Loos BG. Systemic markers of inflammation in periodontitis. J Periodontol. 2005;76(11 Suppl):2106-15. [DOI: 10.1902/jop.2005.76.11-S.2106]
6. Patil NA, Patil SA, Kale VT, Kamble PS, Wasawade HS, Sunil R. Association between Serum Albumin Levels and Periodontal Disease.J Res and Advancement in Dentist.2015;4:27-31. [Link]
7. Amitha R, Mary JA, Biju T, Kumari S, Fathimath N. Association of Serum Albumin Concentration and Periodontitis.IRJP.2012;3: 183-6. [Link]
8. Saravanan AV, Mythili SR, Panishankar KH and Pradeep K. Estimation of serum Albumin Levels associated with Chronic periodontitis in Elderly Subjects-A cross sectional study.Streamdent Journal.2012;3:120-5. [Link]
9. Kolte RA, Kolte AP, Kohad RR. Quantitative estimation and correlation of serum albumin levels in clinically healthy subjects and chronic periodontitis patients. J Indian Soc Periodontol. 2010;14(4):227-30. [DOI: 10.4103/0972-124X.76923]
10. Marcaccini AM, Meschiari CA, Sorgi CA, Saraiva MC, de Souza AM, Faccioli LH, Tanus-Santos JE, Novaes AB, Gerlach RF. Circulating interleukin-6 and high-sensitivity C-reactive protein decrease after periodontal therapy in otherwise healthy subjects. J Periodontol. 2009;80(4):594-602. [DOI: 10.1902/jop.2009.080561]
11. Pradeep AR, Anuj S. Anemia of chronic disease and chronic periodontitis: does periodontal therapy have an effect on anemic status? J Periodontol. 2011;82(3):388-94. [DOI:

10.1902/jop.2010.100336]

12. Lobão WJM, Carvalho RCC, Leite SAM, Rodrigues VP, Batista JE, Gomes-Filho IS, Pereira ALA. Relationship between periodontal outcomes and serum biomarkers changes after non-surgical periodontal therapy. An Acad Bras Cienc. 2019;91(2):e20170652. [DOI: 10.1590/0001-3765201920170652]
13. Stine Jacobsen.Review of Equine Acute-phase Proteins.Medicine Infectious Disaeses.2007;53:230-5. [Link]
14. Kaur N, Kaur N, Sarangal V. A study to evaluate the correlation of serum albumin levels with chronic periodontitis. Indian J Dent Res. 2015;26(1):11-4. [DOI: 10.4103/0970-9290.156788]
15. Lalkota H, Alluri LSC, Da Silva APB, Gummalla S, Kondareddy KMR. Estimation and Correlation of Serum Albumin and Serum Alkaline Phosphatase Levels Between Smokers and Non-smokers With Generalized Chronic Periodontitis. Cureus. 2021;13(8):e17474. [DOI: 10.7759/cureus.17474] [PMID] [PMCID]
16. khoshhal M, Mortazavi H, Saghafi S, jamshidi Z. Abdolsamadi H. Evaluation of Serum albumin Level in chronic periodontitis.journal of mashhad dental school.2010;38(3):189-96. [DOI: 10.22038/JMDS.2010.1186]
17. Shirmohammadi A, Faramarzi M, Salari A, Sadighi Shamami M, Babaloo AR, Mousavi Z. Effect of non-surgical periodontal treatment on serum albumin levels in patients with chronic periodontitis. J Adv Periodontol Implant Dent. 2018;10(1):18-23. [DOI: 10.15171/japid.2018.004] [PMID] [PMCID]
18. Ashtankar MA, Dixit MB, Pimpale SK. Evaluation Of serum albumin concentration in Generalized Chronic Periodontitis patients after surgical periodontal therapy. Indian J Multidiscip Dent. 2019;9(2):77-82. [DOI:10.4103/ijmd.ijmd_29_19]
19. Wu D, Lin Z, Zhang S, Cao F, Liang D, Zhou X. Decreased Hemoglobin Concentration and Iron Metabolism Disorder in Periodontitis: Systematic Review and Meta-Analysis. Front Physiol. 2020;10:1620. [DOI: 10.3389/fphys.2019.01620]
20. Costa SA, Ribeiro CCC, Moreira ARO, Carvalho Souza SF. High serum iron markers are associated with periodontitis in post-menopausal women: A population-based study (NHANES III). J Clin Periodontol. 2022;49(3):221-29. [DOI: 10.1111/jcpe.13580]
21. Shirmohamadi A, Chitsazi MT, Faramarzi M, Salari A, Naser Alavi F, Pashazadeh N. Effect of non-surgical periodontal treatment on transferrin serum levels in patients with chronic periodontitis. J Dent Res Dent Clin Dent Prospects. 2016;10(3):169-75. [DOI: 10.15171/joddd.2016.027] [PMID] [PMCID]
22. Lira-Junior R, Holmström SB, Clark R, Zwicker S, Majster M, Johannsen G, Axtelius B, Åkerman S, Svensson M, Klinge B, Boström EA. S100A12 Expression Is Modulated During Monocyte Differentiation and Reflects Periodontitis Severity. Front Immunol. 2020;11:86. [DOI: 10.3389/fimmu.2020.00086]
23. Newcomer ME, Jones TA, Aqvist J, Sundelin J, Eriksson U, Rask L, Peterson PA. The three-dimensional structure of retinol-binding protein. EMBO J. 1984;3(7):1451-4. [DOI: 10.1002/j.1460-2075.1984.tb01995.x]
24. Martinez-Herrera M, Silvestre FJ, Silvestre-Rangil J, López-Domènech S, Bañuls C, Rocha M. Levels of serum retinol-binding protein 4 before and after non-surgical periodontal treatment in lean and obese subjects: An interventional study. J Clin Periodontol. 2018;45(3):336-344. [DOI: 10.1111/jcpe.12840]
25. Türer ÇC, Ballı U, Güven B. Fetuin-A, serum amyloid A and tumor necrosis factor alpha levels in periodontal health and disease. Oral Dis. 2017;23(3):379-86. [DOI: 10.1111/odi.12625]
26. Furugen R, Kawasaki K, Kitamura M, Maeda T, Saito T, Hayashida H. Association of low fetuin-A levels with periodontitis in community-dwelling adults. J Oral Sci. 2020;62(1):67-9. [DOI: 10.2334/josnusd.18-0282]
27. Ersin Kalkan R, Öngöz Dede F, Gökmenoğlu C, Kara C. Salivary fetuin-A, S100A12, and high-sensitivity C-reactive protein levels in periodontal diseases. Oral Dis. 2018;24(8):1554-61. [DOI: 10.1111/odi.12927]
28. Nejadi R, Sattari M, Taleghani F. Assessment of Non-surgical Periodontal Therapy on IL-22 and S100A12 Concentration in Gingival Crevicular Fluid. J Clin Diagn Res. 2018;12(12):19-23. [DOI:10.7860/JCDR/2018/35904.12344]