



Periodontitis, Cardiovascular Disease and Fetuin A: A Triad

Raima Bashir¹, Mervyn Hosein², Zil-e-Rubab², Tahir Saghir³ and Fizza Saher^{2*}

¹*Bahria University Medical and Dental College, Sailors Street, Adjacent PNS Shifa, Defense Phase II, Karachi, Pakistan.*

²*Ziauddin Dental/ Medical College, Ziauddin University, S/B, Shahrah - e - Galib, Clifton, Karachi, Pakistan.*

³*National Institute of Cardiovascular Diseases, Rafiqui .H.J.Shaheed Road, Karachi Cantonment, Karachi, Pakistan.*

Authors' contributions

This work was carried out in collaboration among all authors. Authors RB and ZR conceived the idea and concept, RB reviewed the available literature through various search engines, and drafted the article. Authors ZR, FS and MH critically reviewed the manuscript and mentored in formulating the final manuscript. Author TS reviewed the final manuscript.

Article Information

DOI: 10.9734/JAMMR/2021/v33i830887

Editor(s):

(1) Dr.Murali P.Vettath, MEITRA Hospital, India.

Reviewers:

(1) Vinay Marla, India.

(2) J. Martos, Federal University of Pelotas, Brazil.

Complete Peer review History: <http://www.sdiarticle4.com/review-history/67371>

Review Article

Received 03 February 2021

Accepted 08 April 2021

Published 12 April 2021

ABSTRACT

Periodontitis and cardiovascular diseases are two most common and related pathologies which may aggravate each other's pathophysiological impact. Long standing periodontitis leads to a systemic inflammatory response which elicits as well as exacerbates the cardiovascular disease process in the body. Fetuin A is an anti-inflammatory and anti-calcification glycoprotein, the levels of which decrease with ongoing inflammation in the body. Diminished Fetuin A levels due to persistent periodontitis, may promote inflammation and calcification which can predispose to multiple cardiovascular outcomes. Therefore the purpose of this literature review was to critically analyse the studies regarding Fetuin A, periodontal inflammation and cardiovascular diseases and find out a possible relationship between them. The studies published from the year 1976-2020 were reviewed for this article using Google Scholar, Pubmed, Research Gate & Semantic Scholar search engines using key words Periodontitis & Fetuin A, Fetuin A, Alpha-2- Heremans Schmid

*Corresponding author: E-mail: fizza.saher@zu.edu.pk;

Glycoprotein, pathogenesis of cardiovascular diseases, periodontitis and CVD, CVD and Fetuin A, etc. It can hence be concluded from this review article that Fetuin A glycoprotein has a protective effect on the body owing to its anti-inflammatory and anti-calcification properties. It also advocates that decreased levels of Fetuin A can be used as a potential diagnostic tool to assess the predisposing risk of cardiovascular diseases affected by calcification and inflammatory process in the body.

Keywords: Periodontitis; Cardiovascular diseases; Fetuin A; triad.

1. INTRODUCTION

Periodontitis is a microbial associated inflammatory, tissue destructive disease of the periodontium which affects about 743 million people worldwide [1]. The global prevalence of periodontitis is about 57.3 % [2]. Periodontitis occurs as a consequence of dynamic & multiplex interaction of local factors, immune-mediated host responses and environmental factors [3]. Multiple risk factors both modifiable and unmodifiable also contribute to increase the probability of periodontitis [4-5]. The periodontopathogenic bacteria namely *Porphyromonasgingivalis*, *Treponemadenticola*, *Tannerella forsythia*, and *Aggregatibacter actinomycetemcomitans* forming the “red complex” have been strongly linked with several systemic diseases via activation of inflammatory mediators after escaping into the systemic circulation [6]. A number of conditions have been attributed to periodontitis such as cardiovascular diseases, respiratory disease, kidney diseases, metabolic syndrome, rheumatoid arthritis, low birth weight in pregnancy and even cancer [7]. Periodontitis has been proposed to be a risk factor for Cardiovascular disorders (CVD) affecting the vascular system by a dual mechanism. First, by accelerating the overall burden of inflammatory markers related to the bacterial virulence, and alternately/secondly by directly invading the arteries engendering atherogenesis [8-9].

Alpha-2- Heremans Schmid Glycoprotein (AHS2G), also known as Fetuin-A (FA) is a multifunctional hepatic synthesized circulating glycoprotein [10]. Its numerous pathological & physiological effects on various systems of the body such as bone mineralization, metabolism, nervous system and cardiovascular systems (CVS) have been studied [11]. Fetuin-A has anti-inflammatory and anti-calcification properties which owe to the preventive effect that FA has in warding off atheroma formation and atherosclerosis [12]. The elevated levels of inflammatory markers and Matrix metalloproteins

(MMP) generated by systemic inflammation influenced by periodontitis down-regulates the circulating FA. This in turn, decreases its protective effect on CVS predisposing it to the destructive effects of systemic inflammation [13]. The purpose of this review is to highlight the possible relationship between periodontitis, CVD and Fetuin A through previously published articles.

This review focuses on outlining the pathophysiological connection/mechanisms existing between two globally prevalent inflammatory conditions: periodontitis and CVDs. It also aims at seeking a potential diagnostic link and possible protective effects of Fetuin-A (FA) in bridging these two chronic diseases. It will help determine if FA can be used as a potential marker in both these conditions for future studies.

2. DISCUSSION

2.1 Inflammation & Periodontitis

Inflammation is the essence of pathogenesis of periodontal and other systemic inflammatory modulated diseases especially cardiovascular diseases [14]. Inflammation starts off as a physiological response to an agent/insult which, if not eradicated timely converts the inflammation into a pathological or chronic form [15].

Periodontitis displays periods of active and quiescent stages during its progression, and can be managed promptly if treatment is provided [16]. When the periodontal bacteria (microbes) residing in the dental plaque and calculus of the periodontal pockets have accumulated substantially, they cause the release of acute phase proteins, Lipopolysaccharides (LPS), antigens & virulent toxic products (endotoxins) that elicit the body's host immune response [15].

The host-immune mediated inflammatory response, in turn, releases cytokines, prostanoids and Matrix Metalloprotein (MMP)

which leads to the destruction of connective tissues and disturbs bone metabolism of the periodontal tissues leading to clinical signs of periodontal disease development & its progression [15,17]. The inflamed & ulcerated gingival sulcular area produced secondary to host-immune response, acts as a favorable site for leakage of microbial toxins into the blood stream contributing to systemic inflammation [18].

Once in the blood stream these exotoxins and endotoxins disseminate to distant sites of the human body to serve as a mode of systemic infection [19-20]. Cardiovascular diseases, respiratory infections, Diabetes Mellitus, insulin resistance, stroke, Alzheimer's disease, gastrointestinal diseases and unfavourable pregnancy outcomes have all been reported to be associated with the periodontal pathogens [21-22]. This accentuates the facts that the treatment of periodontal diseases should never be ignored and deferred as they predispose the body to multiple systemic diseases.

2.2 Periodontitis and Cardiovascular Disease

Periodontitis plays an independent but contributory role in the initiation and progression of cardiovascular diseases [23]. High global prevalence, sharing of common risk factors and being the product of chronic inflammation are the similarities shared between these two diseases [24]. Experimental animal studies have also indicated that periodontal infections could increase atherosclerosis in the presence or absence of hypercholesterolemia [25].

Meta-analysis, prospective cohort and case-control epidemiological studies have strengthened the notion that an association exists between periodontitis and developing atherosclerotic vascular disease, atherosclerotic plaque disruption, coronary heart disease, and acute myocardial infarction. [26-29]. Furthermore, the course of atherosclerosis is influenced by the persistent low grade inflammation associated with periodontitis [30]. Vascular calcification mediated as a result of chronic inflammatory stress, has been reported to be a powerful indicator of atherosclerosis & other cardiac related mortalities as confirmed by electron beam computed tomography [31]. The density as well as the extent of calcification, is directly proportionate to the accelerated likelihood of cardiovascular events [32-33].

The main periodontal pathogen *Porphyromonas gingivalis* has been found to aggravate chronic inflammation in the vasculature by escaping the innate immune system of the body as well as producing virulent vesicles responsible for thrombus formation and platelet aggregation [34-35]. Furthermore, the various other interlinked routes of systemic inflammation generated by periodontal pathogens includes (i) increase cholesterol & lipid abnormalities. A case-control study by Stephan et al hypothesized that periodontitis leads to an alteration in the plasma lipoproteins levels which promotes atherogenesis [14]. *P. gingivalis* secretes a family of proteases i.e gingipains which have the potential to proteolytically split and modify plasma lipoproteins, (ii) Epithelial Dysfunction. This is attributed by the enhanced expression of adhesive molecules P & E selectin, & vascular cell adhesion molecule-1 (VCAM-1) on the Vascular Smooth Muscle Cells (VSMC) leading to infiltration of monocytes, plus neutrophils into the vessels to accentuate the ongoing chronic inflammatory process [36-37]. Simultaneously increased permeability due to altered shape of endothelial cells, increases entry of Low Density Lipoproteins (LDL) into the VSMC, undergoing oxidation, forming Foam cells paving way for progression of atherosclerosis [38] (iii) release of proinflammatory cytokine such as IL -6, IL-8, TNF α etc and reactive oxygen species (ROS) by polymorphonuclear leukocytes cause VSMC death and orchestrating atherogenesis [39]. All these processes put the human body at a higher risk of developing microcalcification foci in the cardiac vessels eventually resulting in atherosclerosis [39].

2.3 Fetuin A: Alpha-2- Heremans Schmid Glycoprotein

Fetuin A (FA) was first isolated by Pederson as a naturally occurring serum glycoprotein, from bovine fetal serum in 1944, hence the name [13, 40]. It belongs to the cystatin superfamily and is produced majorly by hepatic and adipose tissues. Fetuin A has been recognized as a multifunctional molecule related to its role in metabolic processes, insulin resistance, regulation of adipogenesis and mineralization throughout the body [41]. FA is down-regulated by inflammatory mediators and is a negative acute phase protein [42]. Although multiple functions of FA are still being discovered, its role in inhibition of ectopic calcification especially in vessels, by regulation of calcium and bone

metabolism is of particular interest in periodontitis and cardiovascular diseases.

2.4 The Triad

Through researches spanning over decades, it has been postulated in this article earlier, that periodontitis and cardiovascular disease are related to each other. Fetuin A in comparison has only recently gained popularity (3 decades) due to its multiple protective physiological effects on various systems of the body. The circulating Fetuin A concentration is however, affected (decreased) by uncontrolled inflammatory burden in the body which also hampers its protective function [42]. This review will thus try to showcase two specifically major roles of Fetuin A, the anti-inflammatory and anti-calcification in preventing the two most common, chronic inflammatory conditions namely periodontitis and cardiovascular disorders. It will also alternately underscore how reduced FA concentration can accelerate the initiation and progression of these two interlinked diseases. [Fig. 1]

2.4.1 Anti-inflammatory role of Fetuin A

Fetuin A has been shown to possess strong anti-inflammatory properties by inhibiting the production of proinflammatory cytokines such as tumor necrosis factor (TNF) by spermine and its synthetic analogues [43]. In-vivo anti-inflammatory effect of FA was confirmed by using inflammatory models on rats, rodents and mice by Dziegielewska K.M. et al. [44]. These studies concluded that when additional FA was administered (e.g 20-100mg/kg) in these animals, it brought about a reduction in the inflammatory response along with improving the animals' survival [45]. Fetuin A has also demonstrated the inhibition of high Mobility Group Box-1 protein release (HMGB-1) by the macrophages which are active in chronic inflammation [45]. HMGB-1 is released at a later stage of inflammatory response as a late proinflammatory cytokines which is known to exacerbate systemic inflammation [46]. The calcium-phosphate (CP) crystals generated during periods of continuous inflammation also induce proinflammatory cytokines secretion through stimulation of neutrophils and monocytes/macrophages and additionally by vascular smooth muscle cell death by apoptosis [47-48]. These CP crystals are also hindered from producing proinflammatory mediators by the anti-calcification effects of FA which is discussed as follows.

2.4.2 Anti-calcification role of Fetuin A

The abundant presence of Fetuin A in bone (25% weightage of noncollagenous proteins) suggests its role in mineralization [49-50]. Previous in-vitro study by Schinke T. et al demonstrated the role of Fetuin A in inhibiting the precipitation of hydroxyapatite from solutions supersaturated with calcium and phosphate by subsequent formation of the Fetuin-mineral complex [51]. In an animal study by Christoph Binkert et al it was confirmed that Fetuin A binds to TGF β /BMPs (transforming growth factor beta/ bone morphogenic protein) cytokines in bone marrow cell cultures of rats treated with dexamethasone (dex-RBMC) acting as an antagonist and inhibiting osteogenesis at concentrations >10 pM [52]. Yet another experimental study by Paul A. Price and Lim JE on rats treated with Etidronate reported the production of large amounts of Fetuin-mineral complex (composed of Fetuin A, Gla protein & calcium, phosphate minerals) namely calcioprotein particles (CPP). The CPP which are produced by the precipitation of the hydroxyapatite crystal are then easily removed by the action of macrophages. This is contrary to immediate precipitation that occurred within minutes in the rats samples, in absence of Fetuin. The in-vivo calcification inhibiting property of FA can thus be justified [53]. Hence these studies support the notion that FA serves as a major inhibitor of pathological ectopic calcification [39,53].

Despite the potent role of Fetuin A in counteracting inflammation and ectopic calcification to prevent cardiac diseases, its concentration in the body is threatened by the products of inflammation. As previously noted, it is a negative phase protein and its concentration in the body is affected (decreased) by the inflammatory load in the body [42].

2.4.3 Affect of Matrix Metalloprotein on Fetuin A

Matrix Metalloprotein (MMP) has been identified as a biomarker in chronic periodontitis as well as a signature inflammatory mediator that degrades all extracellular matrices, and is responsible for tissue destruction seen in this condition [54]. Hence it is considered as a diagnostic and prognostic tool in chronic periodontitis [54]. Recent in-vivo studies by Checchi V et al and Schure RS have demonstrated that MMP especially MMP-7 & MMP-3 are capable of binding and degrading Fetuin A (assessed by

Table 1. Tabular representation of researches showcasing a relationship between Fetuin A, Periodontitis & Cardiovascular diseases

Study title	Year of study	Authors	Study outcome
Correlation of Serum Fetuin A and Matrix Metalloproteinase-7 Levels in Periodontitis and the Outcome of Initial Periodontal Therapy on Their Levels - A Preliminary Report	2019	Reena Lobo et al	Higher circulatory Fetuin A level has a protective role and helps in maintaining periodontal tissue homeostasis. The reduction of Fetuin A in Chronic Periodontitis highlights its predictive importance as an anti-inflammatory biomarker. Concurrently, it could pose as one of the possible linking factors between inflammatory conditions and vascular calcifications.
The Enzymology of Fetuin: A Potential Link between Periodontal Diseases and Calcifying Atheromas	2013	R. Schure	By mass spectrometry the presence of novel, MMP-7-mediated cleavage sites in Fetuin were found. Fetuin bound tightly to MMP-7 (kd =2.96 x 10 ⁻⁹ M). The degradation of Fetuin by MMP-7 could explain, at least in part, the apparent association between periodontal diseases and calcifying atheromas.
Impact of matrix metalloproteinases on inhibition of mineralization by Fetuin	2012	R. Schure et al	MMP-7 and, MMP-3, affect the ability of Fetuin to inhibit the formation of hydroxyapatite <i>in vitro</i> . This data suggest that the MMPs increased in inflammatory diseases, such as periodontitis, could affect regulation of mineralization and potentially enhance the risk of calcified atheroma formation.

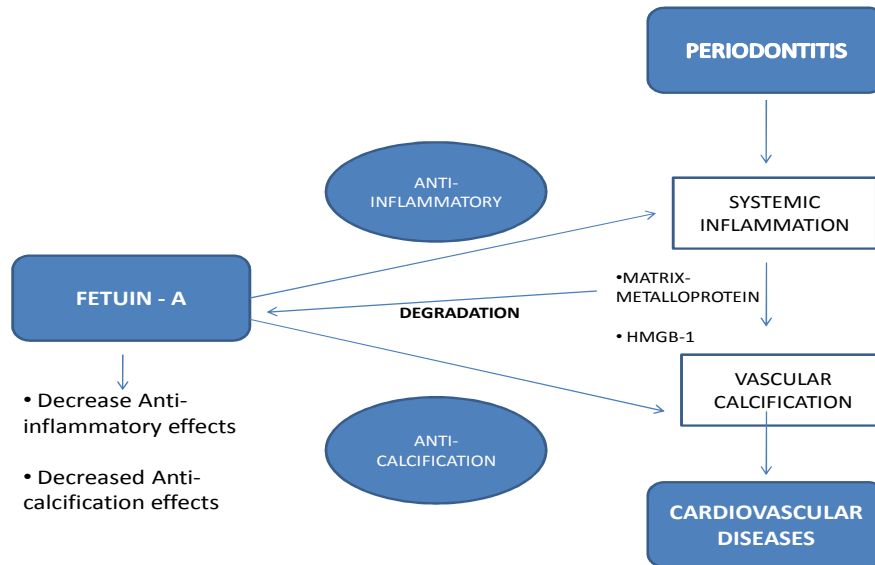


Fig 1. Relationship between periodontitis, cardiovascular diseases (CVD) and Fetuin A

mass spectrometry) in serum of patients with periodontitis, thereby reducing its levels [13,55]. This degradation/destruction of FA in chronic inflammatory conditions deters and even halts the ability of this glycoprotein to carry out its anti-inflammatory and anti-calcification functions needed for the prevention of predisposing cardiac diseases Table 1.

Fig. 1 briefly summarizes the route how periodontitis predisposes to cardiovascular disease. It shows the two most important functions performed by Fetuin A in preventing the spread of inflammation in the body as well as dealing with the ectopic vascular calcification which is the key factor in development of many cardiovascular diseases. This also highlights that the matrix metalloproteinase (MMP) produced by the host-immune response secondary to the systemic inflammation has the capability to degrade Fetuin - A by binding and cleaving the peptide. This leads to a reduction in the circulating Fetuin A levels in the body and hence inhibition of anti-inflammatory and anti-calcification function of Fetuin A which accentuates the inflammatory and calcification processes throughout the body.

3. CONCLUSION

The current literature review suggests a strong association between periodontitis and

cardiovascular diseases as they share multiple similarities in terms of common risk factors, being highly prevalent and debilitating public health conditions. Moreover, it provides a clear understanding of how an oral disease which is usually ignored can influence the initiation and propagation of fatal systemic conditions. This review also provides knowledge about the diagnostic efficiency of a natural glycoprotein Fetuin A, which in higher concentrations has crucial protective and preventive effects on the body especially in the induction and progression of these diseases. This paves the way for its further exploration as a potential diagnostic biomarker. Health care physicians can utilize this piece of information to educate their patients and emphasize better oral hygiene and to maintain a healthy body.

ACKNOWLEDGEMENTS

The contributions and efforts of all authors and fellow postgraduate trainees are highly acknowledged. Special appreciation and gratitude for the supervisor and co-supervisors for their meticulous guidance and valuable suggestions at every step also proof reading and final approval of the article.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Chapple IL, Mealey BL, Van Dyke TE, Bartold PM, Dommisch H, Eickholz P, et al. Periodontal health and gingival diseases and conditions on an intact and a reduced periodontium: Consensus report of workgroup 1 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. *Journal of periodontology*. 2018;89:S74-S84.
2. Jin L, Lamster I, Greenspan J, Pitts N, Scully C, Warnakulasuriya S. Global burden of oral diseases: emerging concepts, management and interplay with systemic health. *Oral diseases*. 2016;22(7):609-19.
3. Albandar JM. Global risk factors and risk indicators for periodontal diseases. *Periodontology*. 2000-2002;29(1):177-206.
4. Anand P, Kamath K, Bansal A, Dwivedi S, Anil S. Comparison of periodontal destruction patterns among patients with and without the habit of smokeless tobacco use—a retrospective study. *Journal of periodontal research*. 2013;48(5):623-31.
5. Chapple IL, Bouchard P, Cagetti MG, Campus G, Carra MC, Cocco F, et al. Interaction of lifestyle, behaviour or systemic diseases with dental caries and periodontal diseases: Consensus report of group 2 of the joint EFP/ORCA workshop on the boundaries between caries and periodontal diseases. *Journal of clinical periodontology*. 2017;44:S39-S51.
6. Hegde R, Awan K. Effects of periodontal disease on systemic health. *Disease-a-Month*. 2019;65(6):185-92.
7. Winning L, Linden GJ. Periodontitis and systemic disease. *BDJ Team*. 2015;2:15163.
8. Łysek RP, Szafraniec K, Polak M, Jankowski P, Micek A, Wolfshaut-Wolak R, et al. Relationship between past myocardial infarction, periodontal disease and Porphyromonas gingivalis serum antibodies: A case-control study. *Cardiology journal*. 2018;25(3):386-92.
9. Nagpal R, Yamashiro Y, Izumi Y. The two-way association of periodontal infection with systemic disorders: an overview. *Mediators of inflammation*; 2015.
10. Dabrowska AM, Tarach JS, Wojtysiak-Duma B, Duma D. Fetuin-A (AHSG) and its usefulness in clinical practice. Review of the literature. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub*. 2015;159(3):352-9.
11. Mori K, Emoto M, Inaba M. Fetuin-A: A multifunctional protein. Recent patents on endocrine, metabolic & immune drug discovery. 2011;5(2):124-46.
12. Lim P, Collet JP, Moutereau S, Guigui N, Mitchell-Heggs L, Loric S, et al. Fetuin-A is an independent predictor of death after ST-elevation myocardial infarction. *Clinical chemistry*. 2007;53(10):1835-40.
13. Schure RS. The Enzymology of Fetuin: A Potential Link Between Periodontal Diseases and Calcifying Atheromas; 2013.
14. Ljunggren S, Bengtsson T, Karlsson H, Starkhammar Johansson C, Palm E, Nayeri F, et al. Modified lipoproteins in periodontitis: a link to cardiovascular disease? *Bioscience reports*. 2019;39(3).
15. Cekici A, Kantarci A, Hasturk H, Van Dyke TE. Inflammatory and immune pathways in the pathogenesis of periodontal disease. *Periodontology*. 2000-2014;64(1):57-80.
16. Gasner NS, Schure RS. Periodontal Disease. *StatPearls [Internet]*; 2020.
17. Jin J, Zhang X, Lu Z, Li Y, Lopes-Virella MF, Yu H, et al. Simvastatin inhibits lipopolysaccharide-induced osteoclastogenesis and reduces alveolar bone loss in experimental periodontal disease. *Journal of periodontal research*. 2014;49(4):518-26.
18. Hirschfeld J, Kawai T. Oral inflammation and bacteremia: implications for chronic and acute systemic diseases involving major organs. *Cardiovascular & Haematological Disorders-Drug Targets (Formerly Current Drug Targets-Cardiovascular & Hematological Disorders)*. 2015;15(1):70-84.
19. Liccardo D, Cannavo A, Spagnuolo G, Ferrara N, Cittadini A, Rengo C, et al. Periodontal disease: A risk factor for diabetes and cardiovascular disease. *International journal of molecular sciences*. 2019;20(6):1414.

20. Muñoz Aguilera E, Suvan J, Buti J, Czesnikiewicz-Guzik M, Barbosa Ribeiro A, Orlandi M, et al. Periodontitis is associated with hypertension: a systematic review and meta-analysis. *Cardiovascular research*; 2019.
21. Tonetti MS, Jepsen S, Jin L, Otomo-Corgel J. Impact of the global burden of periodontal diseases on health, nutrition and wellbeing of mankind: A call for global action. *Journal of clinical periodontology*. 2017;44(5):456-62.
22. Bui FQ, Almeida-da-Silva CLC, Huynh B, Trinh A, Liu J, Woodward J, et al. Association between periodontal pathogens and systemic disease. *Biomedical journal*. 2019;42(1):27-35.
23. Chistiakov DA, Orekhov AN, Bobryshev YV. Links between atherosclerotic and periodontal disease. *Experimental and Molecular Pathology*. 2016;100(1):220-35.
24. Friedewald VE, Kornman KS, Beck JD, Genco R, Goldfine A, Libby P, et al. The American Journal of Cardiology and Journal of Periodontology editors' consensus: Periodontitis and atherosclerotic cardiovascular disease. *Journal of periodontology*. 2009;80(7):1021-32.
25. Paquette DW, Brodala N, Nichols TC. Cardiovascular disease, inflammation, and periodontal infection. *Periodontology*. 2000-2007;44(1):113-26.
26. Stewart R, West M. Increasing evidence for an association between periodontitis and cardiovascular disease. *Am Heart Assoc*; 2016.
27. Gorska R, Dembowska E, Konopka TP, Wysokińska-Miszczuk J, Pietruska M, Ganowicz E. Correlation between the state of periodontal tissues and selected risk factors for periodontitis and myocardial infarction. *Advances in Clinical and Experimental Medicine*. 2017;26(3):505-14.
28. Yu YH, Chasman DI, Buring JE, Rose L, Ridker PM. Cardiovascular risks associated with incident and prevalent periodontal disease. *Journal of clinical periodontology*. 2015;42(1):21-8.
29. Zeng X-T, Leng W-D, Lam Y-Y, Yan BP, Wei X-M, Weng H, et al. Periodontal disease and carotid atherosclerosis: A meta-analysis of 17,330 participants. *International journal of cardiology*. 2016;203:1044-51.
30. Nordendahl E, Gustafsson A, Norhammar A, Näsman P, Rydén L, Kjellström B. Severe periodontitis is associated with myocardial infarction in females. *Journal of dental research*. 2018;97(10):1114-21.
31. Budoff MJ, Shaw LJ, Liu ST, Weinstein SR, Tseng PH, Flores FR, et al. Long-term prognosis associated with coronary calcification: Observations from a registry of 25,253 patients. *Journal of the American College of Cardiology*. 2007;49(18):1860-70.
32. Mori H, Torii S, Kutyna M, Sakamoto A, Finn AV, Virmani R. Coronary artery calcification and its progression: what does it really mean? *JACC: Cardiovascular Imaging*. 2018;11(1):127-42.
33. Rumberger JA, Brundage BH, Rader DJ, Kondos G, editors. *Electron beam computed tomographic coronary calcium scanning: A review and guidelines for use in asymptomatic persons*. Mayo Clinic Proceedings, Elsevier; 1999.
34. Slocum C, Coats SR, Hua N, Kramer C, Papadopoulos G, Weinberg EO, et al. Distinct lipid a moieties contribute to pathogen-induced site-specific vascular inflammation. *PLoS Pathog*. 2014;10(7): e1004215.
35. Herzberg MC, Meyer MW. Effects of oral flora on platelets: Possible consequences in cardiovascular disease. *Journal of periodontology*. 1996;67:1138-42.
36. Lönn J, Ljunggren S, Klarström-Engström K, Demirel I, Bengtsson T, Karlsson H. Lipoprotein modifications by gingipains of *Porphyromonas gingivalis*. *Journal of periodontal research*. 2018;53(3):403-13.
37. Salas-Salvadó J, Casas R, Urpi-Sardà M, Sacanella E, Arranz S, Corella D, et al. *Anti-Inflammatory Effects of the Mediterranean Diet in the Early and Late Stages of Atheroma Plaque Development*; 2017.
38. Wang T, Butany J. Pathogenesis of atherosclerosis. *Diagnostic histopathology*. 2017;23(11):473-8.
39. Shanahan CM. Inflammation ushers in calcification: a cycle of damage and protection? : *Am Heart Assoc*; 2007.
40. Pedersen KO. Fetuin, a new globulin isolated from serum. *Nature*. 1944;154(3914):575.
41. Pan X, Wen SW, Bestman PL, Kaminga AC, Acheampong K, Liu A. Fetuin-A in Metabolic syndrome: A systematic review and meta-analysis. *PloS one*. 2020;15(3):e0229776.

42. Lobo R, Prabhuji M, Karthikeyan B, Greeshma C. Correlation of Serum Fetuin A and Matrix Metalloproteinase-7 Levels in Periodontitis and the Outcome of Initial Periodontal Therapy on Their Levels-A Preliminary Report; 2019.
43. Jahnen-Dechent W, Heiss A, Schäfer C, Ketteler M. Fetuin-A regulation of calcified matrix metabolism. *Circulation research*. 2011;108(12):1494-509.
44. Dziegielewska K, Andersen N. The fetal glycoprotein, fetuin, counteracts ill-effects of the bacterial endotoxin, lipopolysaccharide, in pregnancy. *Neonatology*. 1998;74(5):372-5.
45. Li W, Zhu S, Li J, Huang Y, Rongrong Z, Fan X, et al. A hepatic protein, fetuin-A, occupies a protective role in lethal systemic inflammation. *PloS one*. 2011;6(2):e16945.
46. Wang H, Ward MF, Sama AE. Novel HMGB1-inhibiting therapeutic agents for experimental sepsis. *Shock (Augusta, Ga)*. 2009;32(4):348.
47. Terkeltaub RA, Santoro DA, Mandel G, Mandel N. Serum and plasma inhibit neutrophil stimulation by hydroxyapatite crystals. evidence that serum α 2-hs glycoprotein is a potent and specific crystal-bound inhibitor. *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology*. 1988;31(9):1081-9.
48. Ewence AE, Bootman M, Roderick HL, Skepper JN, McCarthy G, Epple M, et al. Calcium phosphate crystals induce cell death in human vascular smooth muscle cells: a potential mechanism in atherosclerotic plaque destabilization. *Circulation research*. 2008;103(5):e28-e34.
49. Triffitt J. Plasma proteins present in human cortical bone: enrichment of the α 2HS-glycoprotein. *Calcified tissue research*. 1976;22(1):27-33.
50. Termine JD, Belcourt AB, Conn KM, Kleinman H. Mineral and collagen-binding proteins of fetal calf bone. *Journal of Biological Chemistry*. 1981;256(20):10403-8.
51. Schinke T, Amendt C, Trindl A, Pöschke O, Müller-Esterl W, Jahnen-Dechent W. The serum protein α 2-HS glycoprotein/fetuin inhibits apatite formation in vitro and in mineralizing calvaria cells: a possible role in mineralization and calcium homeostasis. *Journal of Biological Chemistry*. 1996;271(34):20789-96.
52. Binkert C, Demetriou M, Sukhu B, Szweras M, Tenenbaum HC, Dennis JW. Regulation of osteogenesis by fetuin. *Journal of Biological Chemistry*. 1999;274(40):28514-20.
53. Price PA, Lim JE. The inhibition of calcium phosphate precipitation by fetuin is accompanied by the formation of a fetuin-mineral complex. *Journal of Biological Chemistry*. 2003;278(24):22144-52.
54. Sapna G, Gokul S, Bagri-Manjrekar K. Matrix metalloproteinases and periodontal diseases. *Oral diseases*. 2014;20(6):538-50.
55. Checchi V, Maravic T, Bellini P, Generali L, Consolo U, Breschi L, et al. The role of matrix metalloproteinases in periodontal disease. *International Journal of Environmental Research and Public Health*. 2020;17(14):4923.

© 2021 Bashir et al.; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Peer-review history:

The peer review history for this paper can be accessed here:
<http://www.sdiarticle4.com/review-history/67371>