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Review Article

Chronic Inflammation as A Link Between Periodontitis and Systemic AA Amyloidosis : A Troubling Connection

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Abstract

Periodontitis is characterized by a chronic inflammation produced in response to a disease-associated multispecies bacterial community in the subgingival region. Although the inflammatory processes occur locally in the oral cavity, several studies have determined that inflammatory mediators produced during periodontitis, as well as subgingival species and bacterial components, can disseminate from the oral cavity, contributing therefore, to various extraoral diseases like systemic AA amyloidosis. Interestingly, amyloidosis associated with periodontal species has been observed in both the oral cavity and extra oral sites. A few studies were showing a strong association between amyloidosis and poor oral health, presence of periodontitis –associated bacteria, tooth loss and clinical signs of periodontitis. Proinflammatory pathways are activated either by mono-or polymicrobial infections, resulting in an increase in the expression of proinflammatory molecules such as IL-6,IL-8,IL-1β and TNF-α. In addition, it has been shown that several periodontitis –associated species induce the expression of genes related to cell proliferation, cell cycle, apoptosis, transport and immune and inflamatory responses. Intriguinly, many of these pathways are linked to systemic AA amyloidosis. Periodontitis can increase the levels of acute-phase reactans and potentiate the development of amyloidosis either by themselves or association with traditional factors, such as familial Mediterranean fever and other chronic inflammatory diseases. Thus, preventing or treating periodontitis might prevent or at least alleviate the progression of amyloidosis. Periodontal evaluation should be performed as part of a medical assessment and considered as an etiologic factor for secondary amyloidosis. It is hoped that medical, dental practitioners, and other health-care professionals will be familiar with perio-systemic link and risk factors, and need to refer to the specialized dental care.

INTRODUCTION

Periodontal diseases are prevalent both in developed and developing countries and affect about 20-50% of global population [1]. High prevalence of periodontal disase in adolescentes, adults and older individuals makes it a public health concern. Several risk factors such as smoking, poor oral hygiene, diabetes, medication, age, hereditary and stress are related to periodontal diseases[1]. Periodontal diseases are dysbiotic conditions in the gingival margin, which are characterized by an imbalance between subgingival communities and the host immune response[2] . Such diseases include gingivitis, which is a reversible condition characterized by the inflammation of the gingiva driven by the combined effect spesific microbial taxa. If not treated, gingivitis could progress to periodontitis, characterized by the destruction of supporting tissues of the teeth. From the progression from gingivitis to periodontitis, several ecological succession occur in the subgingival microbiome, leading to both an increased biomass and the establishment of distinct dysbiotic communities. Interestingly, not only local effects in the oral cavity have been associated with such disorders but also periodontitis has been largely considered as a risk factor for a number of both oral and systemic disease [1-3] .

Although periodontal disease is considered an infectious disease, there is no single bacterial species or group of microorganisms whose mere presence leads to the disease, but rather a shift in the microbial ecology of the dental plaque biofilm that may account for disease progression. Dental plaque in health and in disease is well-organized and complex multicellular ecosystem that contains over 600 different aerobic and anaerobic bacteria [4]. The composition shifts from a predominantly gram-positive aerobic flora in health to a gram-negative and anaerobic flora in disease. The group of bacteria that has been mostly associated with disease is referred to as the ''red cluster'' group and includes *Porphyromonas gingivalis*, *Tannerella forsythia* and *Treponema denticola* [5]. Nevertheless, most of the oral organisms that are associated with disease are also present in low numbers in health, indicating that in biofilm-induced disease states, several commensal organisms appear to emerge as opportunistic pathogens to cause disease in genetically susceptible individuals.

In fact, periodontal pathogens and their products, as well as inflammatory mediators produced in periodontal tissues, might enter the bloodstream, causing systemic effects and/or contributing to systemic diseases [6-10].

The cause of these common inflammatory conditions is the dental plaque. In 1 mm^3 of dental plaque weighing approximately 1 mg more than 10^8 bacteria are present and over 300 species have been isolated and characterized in these deposits. Normally, the oral microbial community and the host immune

response are in equlibrium which allow for periodontal health to be maintained, but pathology can occur when the balance is compromised for several causes:

A: Modification of the environmental conditions of the site, caused by either bacterial interactions or accumulation of dental plaque;

B: Reduction in the proportion of beneficial bacteria, such as those producing inhibitory substances, caused by bacterial interaction or the use of systemic antibiotics; and

C: Deficit of the host immune system

The progression from gingivitis to periodontitis by periodontal pocket development, which favours further plaque accumulation and a shift in its qualitative composition. Periodontitis is associated with different bacteria [11].

Periodontal Infection and Systemic Diseases

In July 1998, the American Academy of Periodontology launched an effort to educate the public about new discoveries: infections in the mouth may play an important role in disorders involving other parts of the body [9]. Periodontal pathogens, as well as their toxins, such as cytolitic enzymes and lypopolisaccharide [LPS] may have access to the blood stream through the compromised and/or ulcerated epithelium of the periodontal pocket. Moreover, within the inflammed gingival tissue a number of inflammatory mediators, such as tumor necrosis factor –alpha [TNF –α], interleukin [IL] 1β, prostoglandin E2 [PGE2] and gamma –interferon are produced; these can enter the blood stream and contribute to the global inflammatory burden. Thus, the systemic exposure to periodontal pathogens, their toxins and periodontal derived/elicited inflammatory mediators may determine pathologic consequences in different organ or systems. Three mechanisms by which periodontal infection may influence systemic health have been described:

1-metastatic infection caused by translocation of gram-negative bacteria from the periodontal pocket to the bloodstream;

2-metastatic injury, such as vascular lesions from the effects of circulating microbial toxins and pro-inflammatory mediators;

3-metastatic inflammation due to the immunological response to the periodontal pathogens and their toxins [12].

On the basis of epidemiological studies the association between chronic periodontitis and cardiovascular disease, respiratory diseases, diabetes, osteoporosis [13], preterm low birth weight [14] and more recently, pancreatic cancer [15], metabolic syndrome [16], chronic kidney disease [17,18], rheumatoid arthritis [19] and neurodegenerative diseases such as Alzheimer's disease [20] has been proposed.

Periodontal disease and systemic inflammation

The pioneering approach of periodontal medicine has helped to renew attention on the theory of focal infection and deepening of the relationship between chronic periodontitis and systemic health. Periodontal evaluations are normally not performed as part of medical assessment. Hence, periodontal diseases may be an overlooked source of inflammation in amyloid patients. However, the anagrommatic question of causal or causal association between infectious diseases and inflammatory changes is distant body sites was never satisfactorily addressed.

Despite the localized nature of periodontal disease a plethora of systemic markers of this condition have been reported and speculated to contribute to systemic diseases[21]. In health, the epithelial barrier in the oral cavity together with the protective innate immune molecules inhibit oral bacteria from entering into the tissues and the bloodstream and therefore in health only small numbers of mostly facultative bacteria enter the circulation[12]. With the advent of periodontal disease it is speculated that the inflammed and ulcerated subgingival packet epithelium forms an easy port of entry for dental plaque bacteria, many of which are gram – negative and obligate anaerobic. Bacteremia in periodontitis has been reported after oral examination and periodontal pathogens have been shown to colonize distant sites [12, 22]. Additionally, bacterial components, such as major outer membrane proteins and endotoxins [i.e.,LPS], may be disseminated. Gram-negative organisms release LPS and endotoxin that can trigger significant systemic inflammation. In response to the bacteremia and bacterial antigens that are systemically dispersed, white blood cells as well as tissue cells at locations where the antigens are relocated, such as endothelial cells and hepatocytes, may produce proinflammatory immune mediators. Furthemore, the locally produced proinflammatory mediators, such as IL-1β, TNF-α,IL-6 and PGE2 may ''spill'' into the circulation and exert systemic or distant effects. The systemic cellular and molecular markers of inflammation in periodontitis include among others an increase of the number of peripheral leukocytes and an increase in the levels of cytokines and acute-phase proteins [23].

A cross –sectional study has demonstrated that plasma levels of inflammatory markers such as C-reactive protein, fibrinogen, interleukins and leucocyte counts increase in periodontitis patients when compared to periodontally healthy patients [24]. Studies reported decrease in both IL-6 and CRP six months after initial periodontal therapy alone [25]. Taken together, these studies suggest that periodontitis can elevate acute-phase reactans [APRs] and other systemic markers of inflammation and effective periodontal therapy may decrease acute-phase reactan [APR] values. Subgingivally located bacteria and bacterial components and products, especially endotoxins, may easily enter the blood circulatory system via the infected and injured epithelium of deepened gingival pockets as well as after daily oral hygiene routins. Even gentle mastication leads to increased release of bacterial endotoxins into the peripheral blood [26]. Such bacterial release as well as systemic inflammation induced by local inflammation mediators, very likely occurs in periodontitis patients, not just transiently but also long-term. Continuous exposure to several periodontal pathogens fits well with the theory of the role of infections in systemic AA amyloidosis. Total pathogen burden, the number of pathogens and endotoxemia, the concentration and activity of the endotoxins to which an individual has been exposed, may contribute to amyloidosis. The

systemic immune response, genetic factors and environmental factors also affect the risk of developing periodontitis [27] and systemic AA amyloidosis[28].

Periodontitis is characterized by a chronic inflammation produced in response to disase-associated multispecies bacterial community in the subgingival region. Although the inflammatory processes occur locally in the oral cavity ,several studies have determined that inflammatory mediators produced during periodontitis, as well as subgingival species and bacterial components, can disseminate from oral cavity, contributing therefore, to various extraoral like amyloidosis. Interestingly, amyloidosis associated with periodontal species has been observed in both the oral cavity and in extra oral sites [29-33].

Periodontal Disease and Systemic Amyloidosis

Periodontal diseases are moving into the focus of systemic diseases. Periodontitis is a chronic and occult infection. The hypothesis is that periodontitis should be considered as a possible etiological factor along with the traditional factors for systemic AA amyloidosis.

Deposition of amyloid fibrils derived from circulating APR serum amyloid A protein [SAA] causes systemic AA amyloidosis, a serious complication of many chronic inflammatory disorders. It has been demonstrated biochemically that AA amyloidosis results from abnormal accumulation of proteins which are deposited as insoluble fibrils in extracellular tissue, leading to the disruption of their normal function. Although recent decades have provided significant advances in our understanding of the pathology and pathogenesis of AA amyloidosis, the mechanism and physical factors promoting AA amyloidosis are largely unknown [28,34-39]. Its pathogenesis is multifactorial involving many variables such as the primary structure of the precursor protein, the acute –phase response, the presence of non-fibril proteins receptors, lipid metabolism proteases [28]. The modern classification of amyloidosis is based on the nature of the precursors plasma proteins that form the fibril deposits and divided into two types: primary amyloidosis and secondary amyloidosis [28]. Secondary amyloidosis is caused by amyloid derived from SAA, an acute phase protein produced in response to inflammation [28,34,35]. Approximately 45% of cases of systemic amyloidosis are secondary or reactive [AA] amyloidosis. Among the causes of AA amyloidosis are various chronic inflammatory conditions such as rheumatoid arthritis, sarcoidosis, Chron's disease, ulcerative colitis, tuberculosis, idiopathic diseases and inherited diseases like familial Mediterranean fever [FMF] [34-39]. AA amyloidosis also associated with malignant diseases such as Hodgkin's disease and mesothelioma [35]. The prevalence rates of AA amyloidosis in these disorders show wide variations due in part to geographic differences, possibly genetic factors and also according to the methods of resarch performed by the native biopsises or postmortem studies. The underlying inflammatory disease is usually longstanding and characterized with persistent inflammation. Renal involvement is the major cause of morbidity and mortality in AA amyloidosis [35-39].

It has long been known that AA amyloidosis occurs after a lengthy period of ongoing inflammatory and/or infectious disease. Therefore, AA amyloidosis may not be suspected during the early course of potential chronic or recurrent inflammatory disease. However, in rare cases it may occur within a year of clinically apperent inflammatory disease[28]. AA amyloidosis does not occur in the absence of an acute-phase response or without elevated SAA levels. Synthesis and secretion of acute-phase SAA is mediated by cytokines, mainly in IL-1, IL-6, IL-10 and TNF-**α** [34-39]. During the acute–phase response, the hepatic biosynthesis of SAA is up-regulated by pro-inflammatory and circulating concentrations can increase by up to 1000-fold. Chronically elevated SAA concentrations are a prerequisite for the pathogenesis of AA amyloidosis [40]. It has been reported that mortality, amyloid burden and renal prognosis are all significantly correlated with SAA. The activation pattern and prognostic value of the SAA protein in inflammation is similiar to that of CRP [41,42]. SAA and CRP are both termed first -class APRs since they are the most sensitive plasma proteins indicating inflammatory activity [43,44].

The above reports are significant for patients with AA amyloidosis because elevation is serum inflammatory markers such as CRP,IL-1,IL-6 and TNF- **α** has been reported to be a robust predictor of AA amyloidosis even without obvious infection or inflammation [45,46]. In addition to the fact that localized deposits of amyloid in patients with systemic AA amyloidosis can aggrevate periodontal disease, chronic periodontal diseases may exaggerate AA amyloidosis via increased levels of systemic inflammatory mediators. Indeed, patients with chronic periodontal diseases have higher levels of SAA-the precursor protein of amyloid fiber in AA amyloidosis –than patients without periodontal disease [47]. Therefore, elimination of the local infection associated with periodontal diseases will aid in reducing levels of systemic inflammatory mediators, which may slow the progression of AA amyloidosis [29-33].

Periodontal infections are polymicrobial and result from the accumulation of bacterial plaque and dental calculus at the gingival margin [48]. These infections develop over several years and are often asymptomatic and painless, but may eventually lead to the loss of teeth. Subgingival located bacteria and bacterial components and products, especially endotoxins, may easily enter the blood circulatory system. Such bacterial release, as well as systemic inflammation induced by local inflammation mediators, very likely occurs in patients with periodontitis,not just transiently but also in long term. Continuous exposure to several periodontal pathogens fits with the theory of the role of infections in amyloidosis . Total pathogen burden [the number of pathogens] and endotoxemia [the concentration and activity of endotoxins] to which an individual has been exposed to may contribute to AA amyloidosis. The systemic immune response, genetic factors and environmental factors also affect the risk of developing periodontitis [27,28,35,48].

Although periodontitis and AA amyloidosis have many features in common,to our knowledge the only reports on the subject are the five reports [29-33], most of which have been published only from our center by MI Cengiz et al. [29,31,32].

One of them [29] was a case report that documented secondary amyloidosis, which was supported by the tongue, buccal mucosa and retromolar trigon and renal biopsies, while ruling out known possible etiologic factors as the cause of secondary amyloidosis. This patient developed AA amyloidosis most likely secondary to his long-standing peritonitis. Moreover, this study demonstrated that secondary amyloidosis can be slowed down if periodontal conditions can be improved.

The second study [31], showed that the prevelance of moderate to severe periodontitis in patients with FMF with amyloidosis [80.6 %] was significantly greater than those in patients with FMF without amyloidosis [38%] and control patients [20%]. In addition, serum levels of APRs in patients with FMF were reduced significantly following nonsurgical periodontal therapy.

The third study [32], which analyzed the etiological distribution of 112 patients with systemic AA amyloidosis, showed that FMF [52,7 %] and chronic inflammatory and neoplastic diseases [35,7 %] were the leading causes of systemic AA amyloidosis, while periodontal disease was found in 11,6 % of the patients in the study. The prevalence was 47,5 % in patients with FMF, 72,5 % in patients with chronic inflammatory diseases and 84,7% in patients with periodontal disease. Serum levels of APRs in patients with AA amyloidosis were reduced significantly following nonsurgical periodontal therapy.

Other one of which [30], was a case report that illustrated an interaction between systemic amyloidosis and severe periodontitis in patient with rheumatoid arthritis.

The other one [33], was a short review that contained most of the studies published by our center.

It is suggested that periodontitis may be an important occult source of chronic inflammation that increases the levels of the APRs in these patients and hence might affect the development of AA amyloidosis. Periodontitis can increase the levels APRs and potentiate the development of amyloidosis either by themselves or association with traditional factors, such as FMF and other chronic inflammatory diseases. FMF seems to be the leading cause of AA amyloidosis in Turkey followed by chronic inflammatory diseases [rheumatoid arthritis, tuberculosis, bronchiectasis, chronic osteomyelitis and so forth] and unknown causes. The progression of AA amyloidosis depends on the nature and status of the underlying chronic inflmmatory diseases.

Furthermore, genetic variants of some cytokines confer suscceptibility to periodontitis [49]. In addition, in aggresive periodontitis, genetically determined host responses and microbiological factors appear to be deterministic components, which may trigger or cause the onset of these diseases [50]. These findings support the hypothesis suggesting that complex interactions between the microbiota and the host genome may be the basis of susceptibility to aggresive periodontitis [49,51]. The systemic immune response, and genetic and environmental factors also affect the risk of developing periodontitis and amyloidosis [27,28]. Also, patients with chronic periodontal diseases have higher levels of SAA protein in secondary amyloidosis than patients without periodontal disease [47]. Chronic periodontal disease could exaggerate secondary amyloidosis via increased levels of systemic inflammatory mediators. Therefore, elimination of local infection associated with periodontal disease will aid in the reaction of levels of systemic inflammatory mediators; which may slow the progression of secondary amyloidosis. Therefore, if intra-oral biopsies are used more commonly for patients with chronic periodontal disease, amyloid may be found more frequently than expected.

Graziani F et al., conducted a study to determine whether non-surgical periodontal treatment in subjects with generalized chronic periodontitis add some beneficial effect on renal function. Greater increase of CRP and SAA was observed in the first 24 hours and decreased after 30 days of treatment. Periodontal infection with intensive therapy may increase endothelial function and may reduce systemic inflammatory markers acting on the risk of serious diseases [52]. The kinetics of serum inflammatory markers are observed after a course of treatment comprising surgical and non–surgical therapy and periodontal surgeries [53.

The results suggest that SAA and CRP concentrations in patients with chronic periodontitis are comparably elevated. High serum titers of antibodies to *P.gingivalis* and the presence of periodontal disease are independently related to high SAA and CRP levels [43].

The studies presented above show that SAA has only begun to be studied in dentistry. Indeed, patients with chronic periodontal diseases have higher levels of SAA protein in secondary amyloidosis than patient without periodontal disease [43,47] . Chronic periodontal disease could exaggerate secondary amyloidosis via increased levels of systemic inflammatory mediators. In addition, the possibility that amyloid deposition in patients with systemic amyloidosis causes accelerated periodontal destruction and bone loss of affected teeth. Amyloid deposition within the periodontium elicited on inflammatory reaction similar to that of foreign body material. Accelerated destruction of periodontium and associated supporting bone apparently is caused by this foreign –body –type giant cell reaction. Therefore, elimination of local infection associated with periodontal diseases will aid in the reduction of levels of systemic inflammatory mediators, which may slow the progression of secondary amyloidosis.

More recently, a systemic review published in 2020 by AF Brunger et al. [54], a PubMed, Embase and Web of Science literature search were performed on causes of AA amyloidosis published in the last four decades. Initially, 4066 unique titles were identified, but only 795 full-text articles and letters were finally selected for analysis. The presence of AA amyloid was proven in 208 articles [26 % of call] of which 140 [67%] showed a strong association with an underlying disease process. Disease associations were categorized and 48 were listed as strong, 19 as weak, 23 as unclear, and 60 as unlikely. Most newly described diseases are not really unexpected because they often cause longstanding inflammation. Based on the spectrum of identified

causes, a pragmatic diagnostic approach is proposed for AA amyloidosis patient in whom an obvious underlying disease is lacking.

Although gradually more diseases can be tracked down due to improved diagnostic possibilities, an idiopathic rest group remains in which no underlying disease can be detected despite a comprehensive and complete diagnostic search. These cases with an uncertain etiology are referred to as idiopathic AA amyloidosis [55] . The designation idiopathic AA amyloidosis is actually an admission of weakness and the underlying mechanism need clarification. However, in up to approximately 42 % of AA amyloidosis no underlying etiology can be identified [35-39,56,57]. With antimicrobial and immunosuppressive therapies and diagnostic technigues for AA amyloidosis, cases being identified with atypical or unknown cases of inflammation. Therefore, over the last 10 years, there has been a changing face of AA amyloidosis, with decreasing proportion of patients with rheumatologic and infectious and increasing proportion with atypical underlying causes [45,46,57]. Also, patients with atypical underlying disorders had a trend towards better survival [57]. As a result periodontal diseases have not been investigated in systemic AA amyloidosis with unknown etiology.

Periodontal evaluations are not normally performed as a part of the medical assessment of patients with AA amyloidosis. Hence, destructive periodontal diseases may be an overlooked source of inflammation in these patients. Our hypothesis is that periodontal disease may be an important occult source of chronic inflammation that increases the levels of APRs, which in turn, might affect or cause the development of systemic AA amyloidosis. Periodontal disease shares several clinical and pathogenic characteristics with AA amyloidosis. Sustained overproduction of SAA is prerequisite for the development of AA amyloidosis, although the reasons for these remain unknown, Robbins [58] proposed to possible explanations for this. First, SAA protein is normally degraded to soluble end products via monocyte derived enzymes. Conceivably, individuals who develop amyloid have an enzyme defect that cannot breakdown SAA –protein completely hence insoluble AA molecules were produced. Second, a genetically determined structural abnormality in the SAA –protein molecule itself renders it resistant to degradation by monocytes. Evidence has suggested that individual genetic susceptibility to amyloidosis may influence the host's response to infection. Nibali et al. [49] have found the link between polymorphisms of genes encoding for neutrophils receptors and pro-inflammatory cytokines and the presence of pathogenic bacteria in patients with aggresive periodontitis.

The authors then speculated that complex interactions between the microbiota and host genome may be at the basis of a patient's susceptibility to aggressive periodontitis. Currently many investigators are trying to define the genotype –phenotype correlations and risk factors for the development of secondary amyloidosis. Yet, the available literature is sufficient to establish that the periodontal diseases may be a significant risk factor for various systemic disorders, and hence future studies are anticipated to elucidate the mechanism through which the periodontal diseases and systemic diseases affect each other.

CONCLUSION

There are now many studies linking periodontal disease with systemic disease. Meanwhile, a recent consensus reviewed by physicians and dentists recommended that education to encourage improved oral health should be a part of efforts to improve general health. Based on this, we suggest that periodontal evaluation should be performed as a part of the medical assessment of patients with systemic AA amyloidosis. Further research is needed to confirm relationship between chronic periodontitis and number of conditions or systemic diseases, such as AA amyloidosis. Health-care providers should be familiar with perio-systemic link and should be able to diagnose and refer the patients to specialized dental or peridontal care to improve the quality of life of their patients. The current evidence is such that prevention and treatment of periodontal disease may reduce chronic systemic disease risk at both the individual and community level. Periodontal medicine promotes a strong collaboration between dental and medical professionals. Therefore, its diagnosis and management deserve a better interdisciplianary approch.

The medical community should be aware of the potential negative effects of periodontal infection on systemic health. Further research is needed to explore the underlying mechanisms and risk factors of periodontal disease and develop innovative preventive strategies.

REFERENCES

1-Nazir MA (2017) Prevelance of periodontal disease, Its association with systemic diseases and prevention. Int J Health Sci (Qassim) 1: 72-80.

2-Hoare A,Soto C 'Rojas –Celis V,Bravo D. Chronic inflammation as a link between Periodontitis and Carcinogenesis .Mediators Inflamm. 2019; 27: 1-14.

3-Cullinan MP,Ford PJ,Seymour GJ. Periodontal disease and systemic heralth: current status. Australian Dental Journal. 2009; 54 : 562 -569.

4-Socransky SS and Haffajee AD. Dental biofilms :difficult therapeutic targets.periodontology 2000. 2002; 28: 12-55 .

5-Slade GD, Offenbacher S, Beck JD, Heiss G, Pankow JS. Acute –phase inflammatory response to periodontal disease in US population .J Dent Res. 2000 ;79: 49-57.

6-American Association of Endodontists .Oral disease and systemic health:What is the connection? Endodontics :Colleaques for Excellence; Spring/summer 2000.

7-British Dental Association.Endodontic treatment and general health; 1996.

8-Offenbacher S Periodontal diseases:pathogenesis .Ann Periodontal. 1996 :821-878.

9-Scannapieco FA Position paper of the American Academy of Periodontology :periodontal disease as a potential risk factor for systemic disease. J Periodontol. 1998 ; 69: 841-850.

10-Pizzo G,Guiglia R,Russo LL ,Campisi G Dentistry and internal medicine:from the focal infection theory to the periodontal medicine concept. Eur J Intern Med. 2010 ; 21: 496-502.

11-Socransky SS, Haffajee AD Periodontal microbial ecology.Periodontol 2000. 2005;38:135-187.

12-Li X ,Kollveit KM ,Tronstad L, Olsen I Systemic diseases caused by oral-infection.Clin Microbiol Rev. 2000 ;13 :547-558.

13-Kuo LC , Polson AM, Kang T. Associations between periodontal diseases and systemic diseases: a review of the inter- relationships and interactions with diabetes ,respiratory diseases ,cardiovascular diseases and osteoporosis .Public Health. 2008 ;122 :417-433.

14-Offenbacher S, Katz V, Fertik G, CollinsJ, Bayd D, Maynor G, et al. Periodontal infection as a possible risk factor for preterm low birth weight. J Periodontal. 1996 ; 67 :1103-1113.

15-Michaud DS, Joshipura K, Giovannucci E, Fuchs CS, Prospective study of periodontal disease and pancreatic cancer in US male health proffesionals .J Nath Cancer Inst. 2007 17 ;99 :171-175.

16-Lİ P, He L, Sha YQ,Luan QX .Relationship of Metabolic syndrome to chronic periodontitis .J Periodontol. 2009 ;80 :541-549.

17-Craig RG, Interactions between chronic renal disease and periodontal disease. Oral Dis. 2008 ;14 :1-7.

18-Cengiz MI, Bal S, Gökçay S, Cengiz K, Does Periodontal disease reflect atherosclerosis in continuous ambulatory peritoneal dialysis patients.J Periodontol. 2007 ;78 :1926 -1934.

19-Bartold PM, Marshall RI, Haynes DR, Periodontitis and rheumatoid arthritis : a review.J Periodontol. 2005 ;76 :2066 -2074.

20-Kamer AR , Dasanayake AP , Craig RG, Glodzik-Sobanska I, Bry M, deLeon MS. Alzheimer's disease and peripheral infections:the possible contribution from periodontal infections,model and hypothesis .J Alzheimers Dis. 2008;13 :437-449.

21-Moutsopoulos NM,Madianos PN. Low-Grade Inflammation in Chronic Infectious Diseases. Paradigm of Periodontal Infections. Ann N Y Acad Sci.2006 ;1088:251-264.

22-Haraszthy VI , Zambon JJ,Trevisan M,et al.Identifications of periodontal pathogens in atheromatous plaques. J periodontal. 2000 ;71 :1554-1660.

23-Danesh J ,Collins R, Applebly P R. Association of fibrinogen, C- reactive protein, albumın or leukocyte count with coronary heart disease: meta analyses of prospective studies .JAMA. 1998 13;279 :1477 -1482 .

24-Craig RG , Yip JK, So MK , Boylan RJ, Socransky SS, Hoffrajee AD. Relationship of destructive periodontal disease to the acute –phase response J Periodontol. 2003 : 74:1007-1116.

25-D ' Aiuto F, Parkar M, Andreou G, Suvan J, Brett PM, Ready D, Tonetti MS. Periodontitis and systemic inflammation :control of the local infection is associated with a reduction in serum inflammatory markers . J Dent Res. 2004 ;83 :156 -160.

26-D ' Aiuto F ,Nibati L, Parker M ,et al. Short –term effects of intensive periodontal therapy on serum inflammatory markers and cholesterol –J Dent Res. 2005 ;84 :269 -273.

27-Agrawol AA ,Kabley A, Yeltiwar RK ,Purohit HJ.Assesment of single nucleotide polymorphism at IL-1 A + 4845 and IL-1 B+ 3954 as genetic susceptibility test for chronic periodontitis in Maharasthtrian ethnicity.J Periodontol. 2006 ;77 :1515 -1521.

28-Röcken C ,Shakespeare A. Pathology ,diagnosis and pathogenesis of AA amyloidosis Virchows Arch. 2002 ;440 :111-122.

29-Cengiz MI, Wang HL, Yıldız L. Oral involvement in a case of AA amyloidosis: a case report. J Med Case Rep. 2010 30; 4:200.

30- Khoury S, Dusek JJ, Anderson GB, Wigneswaran N. Systemic amyloidosis manifesting as localized, severe perioduntitıs. J Am Dent Assoc. 2004 ; 135 :617-623.

31- Cengiz MI, Bağcı H, Cengiz S, Yiğit S, Cengiz K. Periadontal disease in patients with familial Mediterranean fever from inflammation to amyloidosis J Periodantol Res. 2009 ; 44 :354-361.

32- Cengiz MI, Yayla N, Cengiz K, Bağcı H, Taşkın E. Interaction between periodontal disease and systemic secondary amyloidosis from infommation to amyloidosis. J Perioduntol.2011 ; 82 : 566-574,

33- Gupta J. Amyloidosis of oral cavity – a review. International Journal of pharmacy and Biological sciences. 2018 ; 8 : 566-569.

34- Elimova E, Kisilevsky A, Ancsin JB. Heparan sulfate promates the aggregation of HDL associated serum amyloid A: evidence for proamyloidogenic histidine molecular switch. FASEB J.2009 ;23 :3436- 3448.

35- Lachman HJ, Gaodman HJ, Gilbertson JA, Gallimore JR, Sabin CA, et al. Natural history and outcome in systemic AA amyloidosıs. N Engl J Med. 2007: 7; 356: 2361-2371.

36- Yılmaz M, Unsal A, Sakmen M, et al. Renal involvement in AA amyloidosis: clinical outcomes and survival. Kidney Blood Press Res. 2013 ;37:33-42.

37- Paydaş S. Report of 59 cases of renal amyloidasis Int Urol Nephrol. 1999;31 : 619-631.

38- Ahbap E, Kara E, Sahutoğlu T, Bastürk T, Koç Y, et al. Outcame of 121 patients with renal amyloid a amyloidosis. J Res Med Sci. 2014 ;19 :644- 649.

39- Ayar Y, Ersoy A, Öksuz MF, Ocakoğlu G, Vuruşkan BA, et al. Clinical outcames and survival in AA amyloidosis Patients. Rev Bras Reumatol Engl Ed. 2017 ; 57: 535-544.

40- Jensen LE, Whitehead AS. Regulation of serum amyloid A protein expression during the acute-phase response. Biochem J. 1998 ;334: 489-503.

41- Yalçınkaya F, Çakar N, Acar B, et al. The value of the levels of acute phase reactants for the prediction of familial Mediterranean fever. Associated amyloidosis: a case control study. Rheumatol Int. 2007 ; 27 : 517-522.

42.Liuzzo G, Biasucci LM, Gallimore JR, et al. The prognostic value of c-reactive protein and serum amyloid A protein in severe unstable angina. N Engl J Med. 1994 18; 331: 417-424.

43-Ardila CM ,Guzman IC. Comparison of serum amyloid A protein and C-reactive protein levels as inflammatory markers in periodontitis .J periodontal Implant Sci. 2015 ; 45 :14-22.

44-Yamada T. Serum amyloid A [SAA] : a concise review of biology . assay methods and clinical usefulness. Clin chem Lab Med. 1999 ;37:381-388.

45- Cengiz K. Uncommon aetiology in renal amyloidosis. Acta Clinica Belgica. 2005; 60:109-113.

46- Nasr SH, Schwarz R, D'Agati VO, Markowitz GS. Paraplegia, Proteinuria, and renal failure. Kidney Int. 2006 ;69 :412-415.

47-Glurich I, Grossi S, Albini B, et al. Systemic inflammation in cardiovascular and periodontal disease: comparative study. Clin Diagn Lab Immunal. 2002 :9 :425-432.

48- Pihlstrom BL, Michalowicz BS, Johson NW. Periodontal diseases. Lancet. 2005 19; 366 :1809-1820.

49-Nibali L, Ready DR, Parkar M, et al .Gene polymorphism and prevalence of key periodontal pathogens .J Dent Res. 2007 ;86:416-420.

50-Tonetti MS, Claffley N ,European Workshop in periodontology group C. Advances in the progression of periodontitis and proposal of definitons of a periodontitis case and disease progression for use in risk factor research.Group C consensus reporth of the 5th European Work-shop in Periodontology.J Clin Periodontol. 2005;32 6:210-213.

51-Cengiz MI, Bağcı H, Cengiz K, Periodontal disease and systemic amyloidosis :from inflammation to amyloidosis – a troubling connection .Hypothesis 2012 ;10 :1-5.

52-Graziani F , Cei S ,La Ferla F,et al. Effect of non-surgical periodontal therapy on glomerular filtration rate of kidney :an exploratory trial .J Clin Periodontol. 2010 ;37 : 638-643.

53-Graziani F , Ceis ,Tonetti M, et al .Systemic inflammation following non-surgical and surgical periodontal therapy. J Clin Periodontol. 2010 ;37 :848-854.

54-Brunger AF,Nienhuis HLA ,Bijzet J, Hazenberg BPC .Causes of AA amyloidosis :a systemic review.Amyloid. 2020 ;27 :1-12.

55-Pras M ,Zaretzky J, Frangione B, et al . AA protein in a case of ''primary '' or ''idiopathic '' amyloidosis .Am J Med. 1980 ;68 :291-294.

56-Bunker D, Gorevic P. AA amyloidosis :Mount Sinai experience ,1997-2012. Mt. Sinai J Med. 2012;79 :749-756.

57-Girnius S, Dember L, Doros G, et al. The changing face of AA amyloidosis: a single center experience .Amyloid. 2011 ;18 1 :226-228.

58-Robins SL (1999) Disease of immunity .In pathologic basis of disease (6EDN) Saunders Co ,Philedelphia, USA, 188-259.

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