**Periodontal disease and systemic amyloidosis: From inflammation to amyloidosis — a troubling connection**

Murat Inanç Cengiz\(^1\)*, Hasan Bagci, Kuddusi Cengiz*

It has been demonstrated that chronic inflammatory conditions such as rheumatoid arthritis, sarcoidosis, Crohn’s disease, ulcerative colitis, tuberculosis, idiopathic diseases and inherited diseases like familial Mediterranean fever (FMF)\(^1\)–\(^4\). AA amyloidosis is also associated with malignant diseases such as Hodkin’s disease and mesothelioma\(^5\). The absolute and relative prevalences of the individual diseases associated with AA amyloidosis show significant geographical and temporal differences. With the decline of tuberculosis in the West, chronic rheumatic and idiopathic inflammatory diseases have become the leading causes of AA amyloidosis\(^6\). However, in the Third World and on the Indian subcontinent, chronic infectious diseases such as tuberculosis and leprosy remain the major causes\(^7\). In approximately 6 to 12% of cases of AA amyloidosis, no underlying etiology can be identified. 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. Periodontal diseases have not been investigated in systemic AA amyloidosis with unknown etiology. Our hypothesis is that periodontitis may be an important occult source of chronic inflammation that increases the levels of acute-phase reactants, which, in turn, might affect or cause the development of systemic AA amyloidosis.

**ABSTRACT** It has become increasingly clear in recent years that periodontal disease can cause dramatic increases in the levels of markers of systemic inflammation and can also result in reductions in the levels of these markers. It is also known that amyloid fibril deposits derived from circulating acute-phase reactant serum amyloid A (SAA) lead to systemic AA amyloidosis. Although recent decades have provided significant advances in our understanding of the pathology and pathogenesis of AA amyloidosis, the mechanism and physiological factors promoting AA amyloidosis are largely unknown\(^8\). 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 and proteases\(^5\).

The modern classification of amyloidosis is based on the nature of the precursor plasma proteins that form the fibril deposits and is divided into two types: primary amyloidosis and secondary amyloidosis. Secondary amyloidosis is caused by amyloid derived from serum amyloid A, an acute-phase protein produced in response to inflammation\(^1\)–\(^4\). 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, Crohn’s disease, ulcerative colitis, tuberculosis, idiopathic diseases and inherited diseases like familial Mediterranean fever (FMF)\(^1\)–\(^4\). AA amyloidosis is also associated with malignant diseases such as Hodkin’s disease and mesothelioma\(^5\). The absolute and relative prevalences of the individual diseases associated with AA amyloidosis show significant geographical and temporal differences. With the decline of tuberculosis in the West, chronic rheumatic and idiopathic inflammatory diseases have become the leading causes of AA amyloidosis\(^6\). However, in the Third World and on the Indian subcontinent, chronic infectious diseases such as tuberculosis and leprosy remain the major causes\(^7\). In approximately 6 to 12% of cases of AA amyloidosis, no underlying etiology can be identified. 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. Periodontal diseases have not been investigated in systemic AA amyloidosis with unknown etiology. Our hypothesis is that periodontitis may be an important occult source of chronic inflammation that increases the levels of acute-phase reactants, which, in turn, might affect or cause the development of systemic AA amyloidosis.

**INTRODUCTION** Periodontal diseases are moving into the focus of systemic diseases. Periodontitis is a chronic and occult infection. Our 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 acute-phase reactant serum amyloid A protein (SAA) causes systemic AA amyloidosis, a serious complication of many chronic inflammatory disorders\(^1\)–\(^3\). 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\(^1\). Although recent decades have provided significant advances in our understanding of the pathology and pathogenesis of AA amyloidosis, the mechanism and physiological factors promoting AA amyloidosis are largely unknown\(^8\). 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 and proteases\(^5\).

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**MINI-REVIEW**

Periodontal disease and systemic amyloidosis: From inflammation to amyloidosis — a troubling connection

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of a potential chronic or recurrent inflammatory disease. However, in rare cases it may occur within a year of a clinically apparent inflammatory disease. 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 interleukin-1 (IL-1), IL-6, IL-10 and tumour necrosis factor-alpha (TNF-alpha). The SAA proteins are multifunctional apolipoproteins that are involved in cholesterol transport and metabolism, and in modulating numerous immunological responses during inflammation and the acute-phase response to infection, trauma or stress. During the acute-phase response, the hepatic biosynthesis of SAA is up-regulated by pro-inflammatory cytokines, and circulating concentrations can increase by up to 1000-fold. Chronically elevated SAA concentrations are a prerequisite for the pathogenesis of AA amyloidosis.

Renal dysfunction is the predominant disease manifestation of AA amyloidosis. It has been reported that mortality, amyloid burden and renal prognosis are all significantly correlated with SAA. The synthesis of SAA is largely regulated by inflammation-associated cytokines, peptide hormone signals produced by endothelial cells, lymphocytes and, in particular, activated monocytes and macrophages. The activation pattern and prognostic value of the SAA protein in inflammation is similar to that of C-reactive protein (CRP). The progressive nature of AA amyloidosis largely reflects the persistent nature of the underlying conditions and, due to fluctuations of disease activity, not all patients show evidence of an acute-phase response at the time of diagnosis.

Periodontal disease shares several clinical and etiopathogenic characteristics with AA amyloidosis. Cross-sectional studies have demonstrated that plasma levels of inflammatory markers such as CRP, fibrinogen, IL-1, IL-6 and leukocyte counts increase in patients with periodontitis when compared with periodontally healthy patients. Studies reported decreases in both IL-6 and CRP 6 months after initial periodontal therapy. Taken together, these studies suggest that not only can periodontitis elevate acute-phase reactants of inflammation, but also that effective periodontal therapy may decrease the acute-phase response. The above reports are of significance for patients with AA amyloidosis because elevation in serum inflammatory markers such as CRP, IL-1, IL-6 and TNF-alpha has been reported to be a robust predictor of AA amyloidosis. It is also known that chronic infection or inflammatory disease may cause AA amyloidosis, even without obvious infection or inflammation. In addition to the fact that localized deposits of amyloid in patients with systemic AA amyloidosis can aggravate periodontal disease, chronic periodontal diseases may exacerbate 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.

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.

Periodontal infections are polymicrobial and result from the accumulation of bacterial plaque and dental calculus at the gingival margin. These infections develop over several years and are often asymptomatic and painless, but may eventually lead to loss of teeth. Periodontal infections are widely regarded as one of the most common diseases worldwide, with a prevalence of 10% to 15%. A recent health examination survey from Finland involving 6300 participants revealed that up to 64% of the adult population had deepened gingival pockets associated with periodontitis, and nearly 20% had a severe form of this disease with pocket deeper than 6 mm.

Periodontitis may be linked to a secondary disease by three pathways: infection due to transient bacteria; immunological response; and toxic injury. This fits well with the modern concept of focal infection. One cubic millimeter of dental plaque contains about 100 million bacteria and may serve as a persistent reservoir for potential pathogenic bacteria. 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 dental oral hygiene routines. Even gentle mastication leads to increased release of bacterial endotoxins into the peripheral blood. 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 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 may contribute to AA amyloidosis. The systemic immune response, genetic factors and environmental factors also affect the risk of developing periodontitis.

Although periodontitis and AA amyloidosis have many features in common, to our knowledge the only reports on the subject are the three reports that we have published. One of our studies 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 the secondary amyloidosis. Our patient developed AA amyloidosis, most likely secondary to his long-standing periodontitis. Moreover, this study demonstrated that secondary amyloidosis can be slowed down if periodontal conditions can be improved. Our second study showed that the prevalence 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 acute-phase reactants in patients with
FMF were reduced significantly following nonsurgical periodontal therapy.

Our third study[11], 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 of moderate to severe periodontitis was 47.5% in patients with FMF, 72.5% in patients with known chronic inflammatory diseases and 84.7% in patients with periodontal disease. Serum levels of acute-phase reactants in patients with AA amyloidosis were reduced significantly following nonsurgical periodontal therapy. We suggested that periodontitis may be an important occult source of chronic inflammation that increases the levels of the acute-phase reactants in these patients and hence might affect the development of AA amyloidosis.

The major determinants of individual susceptibility to chronic periodontitis are the host responses to pathogens. Recent data suggest that bacteria and bacterial products present in dental plaque and crevicular fluid can stimulate immune cells to produce and release numerous inflammatory mediators, such as TNF-alpha, IL-1, IL-6, IL-10 and interferons[12]. In patients with chronic periodontitis, the total amount of IL-6 and TNF-alpha in gingival crevicular fluid is increased.[12,13] The genetic cause of AA amyloidosis in patients with FMF is not completely understood. It appears to be associated with MEVF gene M694V homozygosity and differences in serum amyloid A[13-28]. However, there are also reports that do not confirm this association[13,14]. Furthermore, genetic variants of some cytokines confer susceptibility to periodontitis[15]. In addition, in aggressive periodontitis, genetically determined host responses and microbiological factors appear to be determinant components, which may trigger or cause the onset of these diseases[16]. These findings support the hypothesis suggesting that complex interactions between the microflora and the host genome may be the basis of susceptibility to aggressive periodontitis[16]. The systemic immune response, and genetic and environmental factors also affect the risk of developing periodontitis and amyloidosis[17,29]. Periodontitis is such a powerful background infection that it reduces, and even hinders, the antimicrobial efficacy of antibiotics in preventing systemic events. Due to its biofilm nature, mechanical treatment of the disease is necessary for the treatment of periodontal disease because it is resistant to systemic antibiotics alone.

We believe that periodontitis may be an additive factor to traditional etiological factors for systemic AA amyloidosis as well as being a primary etiological factor. Therefore, treating or preventing periodontitis may help alleviate disease burden or may even prevent the development of systemic AA amyloidosis. Based on this, we suggest that periodontal evaluation should be performed as a part of the medical assessment of patients with systemic AA amyloidosis.H

The authors declare no conflicts of interest.

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