J Periodont Res 2009; 44: 354–361

JOURNAL OF PERIODONTAL RESEARCH
doi:10.1111/j.1600-0765.2008.01115.x

Periodontal disease in patients with familial Mediterranean fever: from inflammation to amyloidosis

M. I. Cengiz[1], H. Bagci[2], S. Cengiz[3], S. Yigit[2], K. Cengiz[4]

[1]Department of Periodontology, Ondokuz Mayıs University, Samsun, Turkey, [2]Department of Medical Biology and Genetics, Ondokuz Mayıs University, Samsun, Turkey, [3]Department of Prosthodontics, Faculty of Dentistry, Ondokuz Mayıs University, Samsun, Turkey and [4]Department of Nephrology, Faculty of Medicine, Ondokuz Mayıs University, Samsun, Turkey

Cengiz MI, Bagci H, Cengiz S, Yigit S, Cengiz K. Periodontal disease in patients with familial Mediterranean fever: from inflammation to amyloidosis. J Periodont Res 2009; 44: 354–361. © 2008 The Authors. Journal compilation © 2008 Blackwell Munksgaard

Background and Objective: Familial Mediterranean fever stimulates a very intense acute-phase reactants response and if left untreated eventually leads to amyloidosis. The aim of this study was to determine the prevalence of periodontal disease among patients with familial Mediterranean fever in the Black Sea region in Turkey and to evaluate whether periodontitis is related to amyloidosis in patients with familial Mediterranean fever.

Material and Methods: One-hundred and thirty three patients with familial Mediterranean fever and 50 healthy subjects were included in this study. Periodontal health and disease were evaluated using the gingival index, papillary bleeding index, plaque index and periodontal disease index. The concentrations of serum acute-phase reactants were measured at baseline and at 4–6 wk after completion of the nonsurgical periodontal therapy. Genetic testing for familial Mediterranean fever was performed using the familial Mediterranean fever StripAssay. Kidney biopsy was carried out on all proteinuric patients.

Results: The prevalence of moderate to severe periodontitis in familial Mediterranean fever patients with amyloidosis (80.6%) was significantly greater ($p < 0.01$) than in familial Mediterranean fever patients without amyloidosis (38%) and in controls (20%). Serum levels of acute-phase reactants in familial Mediterranean fever patients were reduced significantly following nonsurgical periodontal therapy ($p < 0.01$).

Conclusion: Periodontal therapy seems to reduce the serum levels of acute-phase reactants in patients with familial Mediterranean fever. Therefore, treating periodontitis might help to alleviate the disease burden in patients with familial Mediterranean fever.

Murat Inanc Cengiz, Department of Periodontology, Ondokuz Mayıs University, Samsun, Turkey
Tel: +90 362 457 5532
Fax: +90 362 457 6041
e-mail: dtinanc@mynet.com

Key words: familial Mediterranean fever; periodontal disease; acute-phase reactants; amyloidosis

Accepted for publication May 9, 2008

Familial Mediterranean fever is an autosomal-recessive disease that primarily affects the population in the Mediterranean basin, including Turks, Armenians, Arabs and Sephardic Jews (1,2). However, sporadic cases of familial Mediterranean fever have been reported in Ashkenazi Jews, Italians, Poles, Germans and other ethnic groups (3). Familial Mediterranean fever is an autoinflammatory disease, characterized by recurrent attacks of fever and serosal inflammation, along with a very intense acute-phase response. The most important complication of familial Mediterranean fever is secondary amyloidosis (AA amyloidosis), which mainly affects the kidneys, causing proteinuria and leading to renal failure (2). While there are some patients with severe disease who do not develop this fatal complication, others acquire amyloidosis only a few years after disease onset. Secondary

amyloidosis also occurs in some familial Mediterranean fever patients with chronic inflammatory conditions and chronic infections. The AA amyloid fibrils in these patients are derived from the circulating acute-phase reactant serum amyloid A protein. The activation pattern of serum amyloid A protein in the presence of inflammation is similar to that of C-reactive protein. Increased levels of C-reactive protein and serum amyloid A protein have been reported to be associated with increased familial Mediterranean fever disease activity, rapid familial Mediterranean fever disease progression and poor outcome in patients (4–6).

The genetic causes of amyloidosis have yet to be completely understood. It seems to be associated with M694V homozygous mutations of the familial Mediterranean fever gene, *MEFV*, and with differences in serum amyloid A (3,7,8). Several investigators claimed that the M694V homozygote genotype was associated with the development of amyloidosis, whereas others have not confirmed this finding (9–14).

Daily treatment with colchicine can prevent fever, serosal inflammation and amyloid deposition, but it does not eradicate familial Mediterranean fever-associated amyloidosis, which can cause chronic renal failure (15). The diagnosis of familial Mediterranean fever is made on the basis of typical clinical findings, appropriate ethnicity, family history and a positive response to colchicine. Mutation analysis of the *MEFV* gene can be helpful in confirming the diagnosis for patients with an atypical presentation. Acute-phase reactants observed in patients with familial Mediterranean fever include, among others, leucocytosis, elevated erythrocyte sedimentation rate, fibrinogen and C-reactive protein (16).

It has been reported that acute-phase reactants are generally elevated during acute attacks of familial Mediterranean fever and return to normal upon clinical remission (17). However, there are articles reports that in some patients, even those using colchicines regularly, the levels of acute-phase reactants remain high in the intervals between acute attacks of familial Mediterranean fever (18), but the nature and source of this inflammation is unclear. Although changes in the salivary concentration of secretory immunoglobulin A and the phagocytic activity of neutrophils in blood from the gingiva has been reported in patients with familial Mediterranean fever (19), the possibility that periodontal inflammation might contribute to increased acute-phase reactant levels in patients with familial Mediterranean fever has not been investigated previously. Periodontitis is a local inflammatory process caused by bacteria and it may be associated with changes in the systemic inflammatory and immune responses (20–22). In fact, several reports have suggested that effective periodontal therapy may result in a decrease of the systemic markers of inflammation (23–25).

Periodontitis and familial Mediterranean fever have many potential pathogenic mechanisms in common. Both diseases have complex causes including genetic and gender predisposition, and might share many risk factors, such as age, education, smoking, social status and stress (26,27). Moreover, both diseases cause the release of inflammatory markers. During the inflammatory response, local cells are stimulated to release acute-phase reactants (16–18,20–25). *Chlamydia pneumoniae* has been found in patients with familial Mediterranean fever and periodontitis (28,29). It is also known that chronic infection or inflammatory disease may cause secondary amyloidosis, even without obvious infection or inflammation (30,31). Chronic inflammation and periodontal microbial burden may predispose patients with familial Mediterranean fever to acute attacks of familial Mediterranean fever or may be associated with amyloidosis in ways proposed for other infections, such as *C. pneumonia*. Both periodontitis and familial Mediterranean fever stimulate very intense acute-phase reactant responses. Therefore, the aim of this study was to determine the prevalence of periodontal disease among familial Mediterranean fever patients in the Black Sea region in Turkey and to evaluate whether periodontitis is related to amyloidosis in patients with familial Mediterranean fever. We also investigated if nonsurgical periodontal therapy in familial Mediterranean fever patients affects the levels of acute-phase reactants.

Material and methods

The study was performed in the Ondokuz Mayıs University, School of Medicine, Department of Nephrology and Department of Medical Biology and Faculty of Dentistry over a 2-year period (from September 2004 to September 2006). The study protocol was approved by the research ethics committee of the Ondokuz Mayıs University. The investigation conformed to the declaration of Helsinki and all participants gave informed consent for participation. Out of more than 500 patients seen in our clinic, 133 M694V homozygous patients were selected to participate in this study based on a definitive diagnosis of familial Mediterranean fever. We only included in our study group patients who were M694V homozygotes with respect to *MEFV* gene mutations, in order to minimize the effect of genetic variation on amyloidosis. Patients with familial Mediterranean fever and control subjects were matched for age and gender as much as possible.

All patients were of Turkish origin and were referred by their physcians for definitive diagnosis and management, genetic study and counseling. These patients had been previously diagnosed with familial Mediterranean fever, but had not been using colchicine regularly. We based our definitive diagnosis of familial Mediterranean fever on the major and minor criteria proposed by Livneh *et al*. (32), which included recurrent attacks of fever with peritonitis, pleuritis or synovitis, favorable response to colchicine, and/or family history of familial Mediterranean fever in a first-degree relative. All patients who were confirmed to have familial Mediterranean fever were prescribed prophylactic colchicine (1.0–1.5 mg) based on body weight. One-hundred and thirty three patients [71 men and 62 women; 83 of whom had familial Mediterranean fever-

associated amyloidosis (AA amyloidosis)] and 50 healthy controls (26 men and 24 women) were included in the study. Eighty-three (62.4%) of the familial Mediterranean fever patients with amyloidosis had proteinuria, 77 (92.6%) had nephrotic syndrome (proteinuria more than 3.5 g/d) and six (7.2%) had already developed chronic renal failure. Following definitive diagnosis, familial Mediterranean fever patients were divided into two groups according to the presence ($n = 83$) or absence ($n = 50$) of amyloidosis. Eighty-three patients with amyloidosis had proteinuria when familial Mediterranean fever was first diagnosed by us. AA amyloidosis was confirmed by immunohistochemical staining. Twenty-one of 83 patients with amyloidosis were completely edentulous. The control group consisted of 50 healthy individuals recruited from people who visited our dental clinic for routine examinations and minor restorative care. Smokers and anyone with other diseases or having systemic and local infection/inflammation (except for periodontal disease) were excluded.

Demographic data were obtained by questionaire. The data pertinent to the major and minor criteria of Livneh *et al.* (32) were retrieved from the patients by direct questioning. None of the patients had received any other medicine within the previous 3 mo and all were free of other medical diseases. None of the patients had received periodontal or general dental care within 1 year prior to the study. All patients received a complete dental examination. Serum acute-phase reactants and periodontal parameters were recorded at baseline, before colchicine therapy was initiated, and were repeated 4–6 wk after completion of nonsurgical periodontal therapy. Nonsurgical periodontal therapy was completed before colchicine therapy was started.

Baseline periodontal measures were performed by a patient-group-blinded calibrated examiner. All periodontal measurements were obtained at six sites on every tooth by the same examiner who also obtained complete medical histories and blood samples. Following periodontal measurement, patients had nonsurgical periodontal treatment performed by a periodontist; this consisted of oral hygiene instructions and subgingival scaling and root planing using local anesthesia and a piezoelectric instrument equipped with fine subgingival tips (Electro Medical Systems, Nyon, Switzerland). None of the patients received antibiotics during the periodontal treatment and all other necessary dental treatments were carried out before completion of periodontal treatment.

All patients were asked not to brush their teeth before the dental examination that was conducted in the dental clinic according to the World Health Organization Oral Health Country/Area Profile Programme (33).

Clinical measures of the periodontal disease included: (i) gingival index (34), (ii) papillary bleeding index (35), (iii) plaque index (36), (iv) periodontal disease index (26,37) and (v) probing pocket depth (33). Briefly, a standard periodontal probe was used to measure gingival bleeding and the periodontal condition at six sites of all teeth in the mouth, except for third molars. Results of the gingival bleeding assessment for each site were categorized into bleeding or no bleeding after gentle probing. Periodontal examination and charting of periodontal probing depths were recorded (Quadrant, Tooth System; ADA, Chicago, IL, USA). Probing depth and loss of attachment were measured using a periodontal probe (UNC-15; Hu-Friedy, Chicago, IL, USA) at six sites per tooth. Two measurements were made at each probing site. First, the distance from the free gingival margin to the cemento–enamel junction was measured to determine attachment levels. Then, the distance from the free gingival margin to the base of the pocket was measured as probing depth. Attachment loss was calculated (33). The periodontal disease index represents the severity of gingivitis and periodontitis (26,35). Scale values for periodontal disease index ranged from 0 to 6. A gingivitis score of 0 indicated no inflammation; a score of 1 indicated mild gingivitis; a score of 2 indicated moderate gingivitis; a score of 3 indicated severe gingivitis; a score of 4 indicated < 3 mm of attachment loss; a score of 5 indicated 3–6 mm of attachment loss; and a score of 6 indicated > 6 mm of attachment loss (38).

Mean gingival index, plaque index, papillary bleeding index and periodontal disease index scores for each patient were obtained by averaging the scores of individual teeth present. Therefore, the highest possible scores for gingival index, plaque index, papillary bleeding index and periodontal disease index were 3, 3, 4 and 6, respectively. To evaluate periodontitis further, patients were stratified into four groups for statistical analysis: no periodontitis (periodontal disease index score ranked from 0 to 3, representing healthy and gingivitis only); mild periodontitis ($3 <$ periodontal disease index score ≤ 4); moderate periodontitis ($4 <$ periodontal disease index score ≤ 5); and severe periodontitis ($5 <$ periodontal disease index score ≤ 6) (38).

Blood and urine samples were obtained from all patients and controls to test for acute-phase reactants. The sampling was performed at least 2 wk after the end of acute familial Mediterranean fever attacks. Erythrocyte sedimentation rate, high sensitive C-reactive protein, fibrinogen (using the clotting time method; Biopool, Ventura, CA, USA), white blood cell count and serum albumin levels were measured. The erythrocyte sedimentation rate was determined using the Westergren method, and the concentration of high sensitive C-reactive protein was determined using immunonephelometry (BN system; Date Behring Inc., Newark, DE, USA). The lowest and the highest detection limits of this test are < 0.15 and up to 62 mg/L, respectively. Protein electrophoresis was carried out using a cellulose acetate method, and the salicysulphonic acid method was used to test for urine protein: trace and higher levels were accepted as proteinuria. Peripheral blood was used for DNA extraction, and *MEFV* genotyping was performed using the familial Mediterranean fever StripAssay, according to the manufacturer's instruction (8,39).

Statistical analysis

Continuous, normally distributed variables were reported as means ± standard deviation. Comparisons of continuous and categorical data between groups were analysed using analysis of variance and chi-square tests, respectively. Bonferroni and Tamhane corrections for multiple comparisons were used with analysis of variance to determine the significance of differences among continuous variables and the severity of periodontitis. All statistical analyses were carried out using SPSS for Windows 11.0 (SPSS® Software, version 11.0; SPSS, Chicago, IL, USA).

Results

Characteristics of the study population

Demographic and clinical features of familial Mediterranean fever patients with and without amyloidosis, and control groups, are shown in Table 1. There was no significant association between amyloidosis and gender ($p > 0.05$). With respect to age at onset, familial Mediterranean fever patients with amyloidosis were significantly younger than familial Mediterranean fever patients without amyloidosis (7.88 ± 1.68 years for completely edentulous familial Mediterranean fever patients with amyloidosis and 7.78 ± 2.10 years for familial Mediterranean fever patients with amyloidosis who had any remaining natural teeth vs. 9.78 ± 2.10 years for familial Mediterranean fever patients without amyloidosis; $p < 0.05$, Table 1). On the other hand, familial Mediterranean fever patients with amyloidosis who were completely edentolous and using dentures were older (37.33 ± 9.02 years) than the patients in the other groups ($p < 0.01$). Even though there was no significant difference with regard to the age of onset of familial Mediterranean fever between patients with amyloidosis who were completely edentulous and those who had any remaining natural teeth (7.88 ± 1.68 vs. 7.78 ± 2.10 years, $p > 0.05$), the levels of acute-phase reactants, with the exception of fibrinogen and albumin in the edentulous group, were lower than the levels of acute-phase reactants in patients who had any remaining natural teeth ($p < 0.01$, Table 1). None of the familial Mediterranean fever patients without amyloidosis was completely edentulous.

Periodontal measures in familial Mediterranean fever patients

Mean scores for the gingival index, papillary bleeding index, plaque index and periodontal disease index are shown in Table 2. Mean scores were higher in familial Mediterranean fever patients with amyloidosis than those in familial Mediterranean fever patients without amyloidosis and controls ($p < 0.01$). Also, the mean scores of familial Mediterranean fever patients without amyloidosis were higher than those of control subjects ($p < 0.05$).

The distribution of periodontal disease severity strata — The distribution of periodontal disease stratified by periodontal disease index scores are shown in Table 3. Moderate to severe periodontitis in familial Mediterranean fever patients with amyloidosis (80.6%) was greather than that in familial Mediterranean fever patients without amyloidosis (38%), and in controls (20%) ($\chi^2 = 2.29$, 51.30, 21.00; $p < 0.01$ respectively).

Severity of the markers of periodontitis and inflammation

According to the severity of periodontitis, the levels of the acute-phase reactants were as follows: the mean erythrocyte sedimentation rate, high sensitive C-reactive protein, fibrinogen and white blood cell count levels were significantly higher, and the mean serum albumin level was significantly lower, in the groups of patients with moderate and severe periodontitis than in healthy controls

Table 1. Demographic, clinical and laboratory characteristics of the patients and controls

Parameters	Patients with amyloidosis		Patients without amyloidosis	Controls	*p*-value
	Not using dentures ($n = 62$)	Using dentures ($n = 21$)	($n = 50$)	($n = 50$)	
Women/men	29/33	8/13	25/25	24/26	> 0.05
Age at diagnosis (years)	30.48 ± 6.58	37.33 ± 9.02[a]	31.96 ± 7.16	29.70 ± 7.13	< 0.01
Age of onset of FMF (years)	7.88 ± 1.68	7.78 ± 2.10	9.78 ± 2.10[a]	< 0.05	
Abdominal pain	62 (100%)	21 (100%)	50 (100%)		
Fever	62 (100%)	21 (100%)	50 (100%)		
ESR (mm/h)	59.45 ± 8.55[a]	30.14 ± 5.10[a]	23.48 ± 3.91[a]	7.18 ± 3.16[a]	< 0.01
CRP (mg/L)	22.69 ± 2.88[a]	14.52 ± 3.15[a]	11.19 ± 2.60[a]	2.76 ± 1.36[a]	< 0.01
Fibrinogen (mg/dL)	347.95 ± 22.15[b]	342.29 ± 25.24[b]	315.74 ± 31	214.12 ± 50.87 < 0.01	
Serum albumin (g/dL)	2.54 ± 0.55[b]	2.56 ± 0.41[b]	3.58 ± 0.16	4.06 ± 0.47	< 0.01
WBC ($\times 10^3$ μL)	10.04 ± 3.49[a]	7.12 ± 0.66	6.05 ± 0.88	6.20 ± 0.94	< 0.01
Renal biopsy	All	All	–	–	
Genotype	M694V/M694V	M694V/M694V	M694V/M694V	Normal	

[a] $p < 0.01$ vs. all the other groups.
[b] $p < 0.01$ vs. FMF patients without amyloidosis and controls.
CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FMF, familial Mediterranean fever; WBC, white blood cell count.

Table 2. Description of periodontal parameters (mean ± SEM)

Parameters	FMF patients with amyloidosis (n = 62)	FMF patients without amyloidosis (n = 50)	Controls	p-value
Gingival index	2.64 ± 0.65[a]	1.34 ± 0.68[a]	0.70 ± 0.78[a]	< 0.01
Papillary bleeding index	2.34 ± 0.63[a]	1.64 ± 0.63[a]	0.86 ± 0.87[a]	< 0.01
Plaque index	1.98 ± 0.63[b]	1.46 ± 0.61[b]	1.30 ± 0.50[b]	< 0.05
Periodontal disease index	4.72 ± 0.54[a]	2.14 ± 1.6[a]	1.30 ± 0.76[a]	< 0.01

[a]$p < 0.01$ vs. all the other groups.
[b]$p < 0.05$ vs. all the other groups.
FMF, familial Mediterranean fever.

Table 3. Distribution of periodontal disease severity in familial Mediterranean fever patients and controls

	Healthy (%)	Mild (%)	Moderate (%)	Severe (%)	Moderate + severe (%)	p-value
FMF with amyloidosis[a] (n = 62)	0 (0)	12 (19.39)	37 (59.67)	13 (20.96)	50 (80.6)	< 0.001
FMF without amyloidosis[b] (n = 50)	3 (6)	28 (56)	17 (34)	2 (4)	19 (38.0)	< 0.001
Controls[c] (n = 50)	25 (50)	15 (30)	10 (20)	0 (0)	10 (20.0)	< 0.001

a–b: $\chi^2 = 22.29$; $p < 0.001$.
a–c: $\chi^2 = 51.30$; $p < 0.001$.
b–c: $\chi^2 = 24.00$; $p < 0.001$.

Table 4. Severity of peritontitis and inflammatory markers

Parameters	Healthy (n = 28)	Mild (n = 5)	Moderate (n = 63)	Severe (n = 15)
ESR (mm/h)	9 ± 2.94[a]	47.34 ± 4.80[a]	51.69 ± 4.99[a]	64.26 ± 6.24[a]
CRP (mg/L)	7.39 ± 1.91[a]	20.21 ± 2.81[b]	21.14 ± 3.66[b]	25.00 ± 1.81[a]
Fibrinogen (mg/dL)	179.54 ± 18.30[a]	269.54 ± 12.07[b]	269.93 ± 13.86[b]	348.66 ± 22.74[a]
Serum albumin (g/dL)	3.89 ± 0.37[a]	3.37 ± 0.49[b]	3.12 ± 0.44[b]	2.24 ± 0.42[a]
WBC (× 10/L)	7.39 ± 1.57[c]	8.92 ± 1.08[c]	11.32 ± 2.42[a]	21.23 ± 5.17[a]

[a]$p < 0.001$ vs. all the other groups.
[b]$p < 0.001$ vs. different from healthy and severe groups.
[c]$p < 0.001$ vs. different from moderate and severe groups.
CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; WBC, white blood cell count.

and in patients with mild periodontitis ($p < 0.001$). The mean levels of all acute-phase reactants in each group were statistically different from each other, but the mean levels of high sensitive C-reactive protein and fibrinogen were not different in the groups of patients with mild and moderate periodontitis ($p > 0.05$; Table 4).

Effect of periodontal therapy on levels ofinflammatory markers in familial Mediterranean fever patients with and without amyloidosis

We observed that after 4–6 wk of therapy, the concentrations of serum acute-phase reactants in familial Mediterranean fever patients with and without amyloidosis were significantly decreased ($p < 0.001$), whereas the levels of serum albumin were increased ($p < 0.05$, Table 5).

Discussion

In this study, we looked at the relationship between familial Mediterranean fever and periodontal disease. Periodontal disease is particularly severe in familial Mediterranean fever patients with amyloidosis ($p < 0.001$, Table 3). We found that amyloidosis was associated with early onset of familial Mediterranean fever and failure to start appropriate treatment. These results are in agreement with other studies reporting that familial Mediterranean fever attacks in patients with amyloidosis begin at an earlier age, supporting the notion that longer periods of untreated inflammation with elevated levels of acute-phase reactants increase the likelihood of amyloidosis (5,10). Furthermore, the mean levels of acute-phase reactants were found to be higher in familial Mediterranean fever patients with amyloidosis than in familial Mediterranean fever patients without amyloidosis, and controls ($p < 0.001$). Even though there was no significant difference, with regard to the age of onset of familial Mediterranean fever, between patients with amyloidosis who were completely edentulous and those who had any remaining natural teeth ($p > 0.05$; Table 1), the levels of acute-phase reactants, with the exception of fibrinogen and albumin, in edentulous group were lower than those in patients who had any remaining natural teeth ($p < 0.01$, Table 1). This seems to indicate that elimination of advanced periodontitis may decrease the levels of systemic inflammation markers. Therefore, treating periodontitis might help to reduce the disease burden in patients with familial Mediterranean fever. Indeed, the serum C-reactive protein levels were found to be lower in edentulous people than in dentate people (21,40). It was also shown that elimination of advanced periodontitis by full-mouth tooth extraction reduces systemic inflammatory and thrombotic markers of cardiovascular risk (40). Thus, it is

Table 5. Inflammatory markers before and after periodontal therapy

Parameters	Patients with amyloidosis (n = 62)				Patients without amyloidosis (n = 50)			
	Before	After	Percentage*	p-value	Before	After	Percentage*	p-value
ESR (mm/h)	59.45 ± 8.55	41.20 ± 5.47	29.89 ± 10.55	< 0.001	23.48 ± 3.91	9.12 ± 2.37	60.57 ± 10.35	< 0.001
CRP (mg/dL)	22.69 ± 2.88	17.29 ± 2.74	23.93 ± 7.17	< 0.001	11.18 ± 2.60	7.32 ± 1.39	33.34 ± 9.31	< 0.001
Fibronogen (mg/dL)	347.95 ± 22.02	301.30 ± 22.02	11.64 ± 5.01	< 0.001	315 ± 31.00	209.35 ± 26.13	33.40 ± 7.58	< 0.001
Serum albumin (g/dL)	2.54 ± 0.55	2.60 ± 0.55	−2.74 ± 8.13	< 0.001	3.56 ± 0.41	3.59 ± 0.41	−0.85 ± 3.03	< 0.005
WBC ($\times 10^3$ mL)	10.04 ± 3.49	7.71 ± 2.27	21.16 ± 9.52	< 0.001	6.08 ± 0.88	5.00 ± 0.45	16.30 ± 10.18	< 0.001

*Variations (in percentages) in parameters measured in patients before and after periodontal therapy.
CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; WBC, white blood cell count.

possible that induction of a systemic inflammatory state may induce a mechanism by which chronic periodontitis increases the risk of familial Mediterranean fever-associated amyloidosis. Mean values of gingival index, plaque index, papillary bleeding index and periodontal disease index were higher in familial Mediterranean fever patients with amyloidosis than in familial Mediterranean fever patients without amyloidosis, and in controls ($p < 0.01$; Table 2). Moreover, the percentage of occurrence of moderate and severe periodontitis in familial Mediterranean fever patients with amyloidosis (80.6%) was greater than in familial Mediterranean fever patients without amyloidosis (38%) and controls (20%).

To our knowledge, this is the first report evaluating the periodontal status of familial Mediterranean fever patients with and without amyloidosis. The analysis of all examined parameters indicates that periodontitis is more severe in familial Mediterranean fever patients with amyloidosis than in familial Mediterranean fever patients without amyloidosis and in control groups ($p < 0.001$, Table 3).

With the exception of albumin, there was a positive correlation between the severity of periodontitis and the levels of acute-phase reactants ($p < 0.001$; Table 4). Serum albumin, a well-known negative acute-phase reactant, remained normal during the familial Mediterranean fever attacks, in contrast to the increase that was observed after the attacks were over (16,41). This is probably because the duration of intense inflammation in familial Mediterranean fever is limited to the brief periods of the attacks. The change in the magnitude of the acute-phase reactants between attacks and attack-free periods has been used as a means of diagnosis of familial Mediterranean fever for some time (42). However, some early reports noted that acute-phase reactants could remain high during the intervals between the attacks. This has led to suggestion that subclinical inflammation continues during the attack-free periods, even in some of those receiving regular colchicine treatment (16,18).

Several studies have reported that periodontitis is associated with an increased systemic inflammatory burden, mediated perhaps through acute-phase reactants (20–22). Interestingly, several reports suggest that effective periodontal therapy may decrease the levels of systemic markers of inflammation (23–25).

In 2005, D'Aiuto *et al.* (23) showed that there was a significant decrease in serum CRP concentrations after treatment of patients with periodontal disease and high CRP levels. Similarly, we also observed that after 4–6 wk of therapy the high serum acute-phase reactants in familial Mediterranean fever patients with and without amyloidosis were decreased significantly ($p < 0.001$), whereas the level of serum albumin was increased ($p < 0.05$, Table 5).

Growing evidence suggests that individual genetic susceptibility may influence the host response to infection. Recently, Nibali *et al.* (43) found that polymorphisms of genes encoding neutrophil receptors and pro-inflammatory cytokines were associated with the presence of pathogenic bacteria in the periodontal pockets of persons with aggressive periodontitis. Moreover they hypothesized that complex interactions between the microbiota and the host genome may be at the basis of susceptibility to aggressive periodontitis. Furthermore, many investigators are trying to define the genotype–phenotype correlations and the risk factors for the development of secondary amyloidosis. Therefore, the influence of unknown environmental factors and/or genetic modifiers should be taken into account in explanations of phenotypic variation of the disease and the development of amyloidosis in patients with familial Mediterranean fever (5,44).

In this study we have shown that periodontitis might be an important source of inflammation in familial Mediterranean fever patients with and without amyloidosis. It is known that chronic infection or inflammation may cause secondary amyloidosis (30,31, 45). Therefore, periodontitis might affect the development of amyloidosis in patients with familial Mediterranean fever.

Periodontitis in patients with familial Mediterranean fever may be a covert source of chronic inflammation that can be managed through effective periodontal therapy. However, whether treatment of moderate to severe periodontitis in familial Mediterranean fever populations will result in decreased levels of serum acute-phase reactants and, more importantly,

a decreased incidence of amyloidosis awaits the results of interceptive clinical trials in this population.

The results of the present study confirm that periodontitis is highly prevalent in familial Mediterranean fever patients, particularly in familial Mediterranean fever patients with amyloidosis, and show a significant association between severe periodontitis and increased levels of acute-phase reactants. Therefore, its diagnosis and management deserve a better interdisiplinary approach. Although most evidence in regard to the relationship between periodontal disease and those systemic conditions is consistently supportive of this notion, more research is needed. In general, larger and more randomized populations and controlled clinical trials will be required to substantiate the correlation of periodontal disease with these systemic conditions.

In conclusion, the prevalence of moderate to severe periodontitis was greater in familial Mediterranean fever patients with amyloidosis than in familial Mediterranean fever patients without amyloidosis. Periodontitis may be an important occult source of chronic inflammation that increases the acute-phase reactant levels in familial Mediterranean fever patients and might affect the development of amyloidosis in patients with familial Mediterranean fever. Treating periodontitis might help to alleviate the disease burden in patients with familial Mediterranean fever.

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