Oral health and oral quality of life in inactive patients with familial Mediterranean fever without amyloidosis

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ABSTRACT

Objectives. *The aim of this study was to investigate oral and general health-related quality of life (QoL) in patients with familial Mediterranean fever (FMF) disease.*

Methods. *In this cross-sectional study, 45 patients with FMF, 50 age- and sex-matched healthy controls (HC), and 50 patients with Behçet's disease (BD) as the disease control group were included. FMF disease activity was evaluated by using the FMF-severity score, as well as with erythrocyte sedimentation rate (ESR), and serum C-reactive protein and fibrinogen levels. Oral health-related QoL and general QoL were evaluated using oral health impact profile-14 (OHIP-14) and Medical Outcomes Short-Form Health Survey Questionnaire 36 (SF-36), respectively.*

Results. *Only the numbers of extracted teeth (4.13±4.72 vs. 1.55±3.6) and filled teeth (2.33±3.19 vs. 0.66±1.46) were significantly higher in FMF group compared to HC group (p=0.005 and p=0.013, respectively). OHIP-14 score was significantly higher in FMF and BD groups compared to HC group. In FMF patients, OHIP-14 score was positively correlated with the number of extracted teeth (r=0.38, p=0.010), while the number of carious teeth was positively correlated with ESR (r=0.43, p=0.003). When FMF patients were sub-classified according to disease severity, no significant difference was observed with respect to oral health status.*

Conclusion. *In patients with FMF, some of the parameters of oral health status were found to be worse compared to HC group. Tooth loss appears to be to be a critical factor contributing to impaired oral QoL. In general, oral health status in FMF patients is better than in BD patients.*

Introduction

Familial Mediterranean fever (FMF) is an autosomal recessive auto-inflammatory disease (AID) characterised by recurrent attacks of fever and inflammation involving mainly serous membranes, joints and skin. It is commonly observed in non-Ashkenazi Jews, Armenians, Turks and Levantine Arabs in Eastern Mediterranean region (1-6), with a prevalence of up to 1/1000–1/250 (7). The major long-term complication is secondary amyloidosis, which might lead to chronic renal failure (1). FMF attacks are accompanied with neutrophilia (1) and high acute-phase responses (3). Colchicine treatment generally decreases the number and severity of clinical attacks (5) and occurrence of amyloidosis (6), however subclinical inflammation may persist in attack-free periods (1, 7). Anaemia, splenomegaly, decreased bone mineral density and ischaemic heart disease may develop as complications of subclinical inflammation in patients with FMF. Environmental factors, especially the amount of microbial exposure and living conditions, might affect the expression, frequency and pattern of the disease manifestations in FMF (4-8). Among these, infectious agents deserve special attention, and potential pathogens in oral cavity may readily contribute to systemic inflammation (9). Indeed, poor oral health, caused by focal oral infection foci, has already been shown to be a risk factor for systemic diseases such as coronary heart disease, diabetes mellitus, chronic renal disease, rheumatoid arthritis (10) and Behçet's disease (11,12). Besides, genetic factors may further increase the negative effects of microbial pathogens. In this context, genetic mutations associated with the host pathogen sensor systems such as toll-like receptors and the inflammasomes might be linked to

the pathogenesis of FMF, characterised by higher sensitivity to endotoxin exposure (13-15). Periodontal bacteria have also been shown to regulate the activation of inflammasome (16, 17). The influence of environmental factors was confirmed by the clinical observation that FMF attacks were lower in Armenians living in the USA compared to those living in their native country. Similarly, FMF disease severity was found to be milder in Turks living in Germany compared to those in Turkey (4).

The quality of life (QoL) is increasingly recognised as an outcome measure for the evaluation of disease course and management strategies in chronic disorders. Several studies have reported that FMF might cause a decrease in general QoL (18, 19); however, to our knowledge, oral health-related QoL has not been previously studied in FMF. Therefore, we aimed to investigate oral health and oral health-related QoL status in patients with FMF.

Materials and methods

In the present cross-sectional study, consecutive 50 FMF patients (M/F: 21/29; mean age: 35.4±10.2 years) fulfilling Tel-Hashomer criteria (20) were selected. Five patients were excluded because of insufficient data and/or inconsistent statements reflecting oral-health related QoL and the remaining 45 FMF patients (M/F:20/25; mean age: 36.66±10.16 years) who had been followed in the Rheumatology Clinic of Ege University (Aegean Region of Turkey), School of Medicine, were included in the present study.

Since impairment both in oral health and oral health-related QoL was previously shown in Behçet's disease (BD), 50 patients with BD diagnosed by International Study Group Criteria (21), sex- and age-matched with FMF group (M/F:21/29, 35.38±11.01 years) were also included as the disease control group in Marmara University Hospitals (Marmara region of Turkey). BD patients had mucocutaneous involvement and were treated with colchicine (1.5 mg/day). Besides, 50 healthy controls (HC) (M/F:21/29, 32.9±9.9 years) were also included. The control group was selected randomly from healthy people. Having no symptoms of any disorder and being no member or close relative of study patient's family were the inclusion criteria for the control group. Healthy controls were matched with regard to age and gender.

Patients with any chronic systemic diseases such as chronic renal disease, diabetes mellitus, chronic psychotic diseases and those on antidepressant therapy were excluded from the study, since these conditions could modify both oral health and oral health-related QoL status.

The medical data of FMF and BD patients, including demographic data, disease duration and treatment modalities, were recorded and physical examinations were performed. Among the FMF group, amyloidosis with renal failure was not present in any patient. Although rectal biopsy was not carried out in all patients, micro albuminuria and clinical symptoms and signs such as diarrhea splenomegaly were followed up for amyloidosis.

Colchicine treatment was reported to be started as soon as the diagnosis of FMF was made. The mean age of diagnosis was 29.36±11.82 years. Considering the onset of FMF symptoms, the delay of diagnosis was calculated as 8.49±11.14 months. The disease severity was determined using the FMF-severity score (F-SS-2) defined by Mor *et al*. in 2005 (21). Accordingly, FMF disease severity was classified as severe or mild depending upon the presence or absence of six different criteria related with disease characteristics, as described in detail elsewhere (21). The mean level of acute-phase reactants, including ESR (mm/h), C-reactive protein (mg/dl) and fibrinogen (mg/dl), were 9.64±10.49, 0.77±1.81 and 382.9±114.14, respectively. All patients had been receiving colchicine treatment and in clinical remission during the study.

Oral health was evaluated by dental and periodontal indices, including probing pocket depth, clinical attachment level, gingival index, the number of extracted teeth, carious teeth and filled teeth (23) and plaque index (Quigley and Hein) (23-25). The higher the plaque index scores, gingival index scores, periodontal pocket depth and clinical attachment levels were, the worse was the oral health.

Questionnaires regarding general and oral health-related QoL were filled in for all the participants. Oral health-related QoL was evaluated by using oral health impact profile-14 (OHIP-14). A five-point Likert-type scale was used in scoring each item of the OHIP-14. Responses were coded as follows: 0="never"', 1="hardly ever", 2="occasionally", 3="fairly often", 4="very often". OHIP-14 finds a score between 0 and 56 points. Higher scores implicate worse oral health-related QoL (26).

General QoL was evaluated using the Medical Outcomes Short-Form Health Survey Questionnaire 36 (SF-36), which is a generic questionnaire with 8 subscales (27). These domains evaluate the health between 0 and 100 points; 0 point shows the worst health status, while 100 points indicate the best health status (27).

All of the questionnaires used for evaluating general and oral health-related issues had been previously translated and validated in Turkish (28, 29). Trained interviewers helped illiterate patients or individuals with visual problems fill in the questionnaires.

The study protocol was approved by the Human Research Ethics Committee of the University of Ege in Izmir and informed consent was taken from all subjects.

Statistical analysis

Statistical analysis was performed using SPSS 11.0 statistics programme (SPSS Inc, Chicago, IL, USA). Analysis of variance (ANOVA), paired *t*-test and independent *t*-test were used for comparing the groups. The relationship between clinical variables and the scores of questionnaires were evaluated by Pearson's correlation test. Nonparametric Kruskall-Wallis, Mann-Whitney U-test and Spearman correlation test were used when the distributions of data were not normal. *p*-value of <0.05 was accepted to be significant.

Results

Oral health

All the data regarding the numbers of extracted teeth, carious teeth, filled

teeth, as well as plaque index scores, gingival index scores, periodontal pocket depth and clinical attachment levels in all three groups are shown in Figure 1.

Based on the F-SS-2 criteria defined by Mor *et al*. in 2005 (22), the FMF patients included in the present study were classified as severe (n=30, 66.6%) or mild (n=15, 33.3%). Considering the whole group of FMF patients, the number of extracted teeth (4.13±4.72) was similar with BD group (3.95±4.17) (p=0.978), but was significantly higher than in HC (1.55±3.6) (p=0.009). In FMF group, the number of filled teeth (2.33±3.19) was significantly higher than in BD (0.89±1.51) and HC (0.66±1.46) groups, p-values being 0.008 and 0.009, respectively. However, there was no significant difference between BD and HC groups (p=0.91). The number of carious teeth in FMF patients (0.77±1.29) was similar to HC group (0.44±1.15) (p=0.498), but was lower than in BD group (1.65±1.71) (p=0.002 and p<0.0001, respectively) (Fig. 1). ESR values correlated positively with the number of carious teeth in FMF (r=0.43 p=0.003).

The plaque index scores in BD, FMF and HC groups were 2.05±1.1, 1.79±0.82, and 1.41±1.0, respectively. Although plaque index score in BD group was significantly higher than in HC group (p=0.006), in FMF group this score was not significantly different from BD or HC groups. The gingival index scores both in FMF (1.21±0.54) and HC (1.49±1.05) groups were significantly lower than in BD group (1.97±1.08) (p<0.0001; p=0.039). In FMF group, periodontal pocket depth (1.97±0.75) and clinical attachment (2.03±0.88) levels were also significantly lower than in BD group (2.79±0.66 and 3.86±1.59) (p<0.0001 for both), but similar to HC group (2.23±0.83 and 2.33±0.9) (p=0.219 and p=0.431) (Fig. 1). No significant difference was observed in oral health status according to disease severity in FMF. No significant correlation was present between the scores of periodontal indices and ESR.

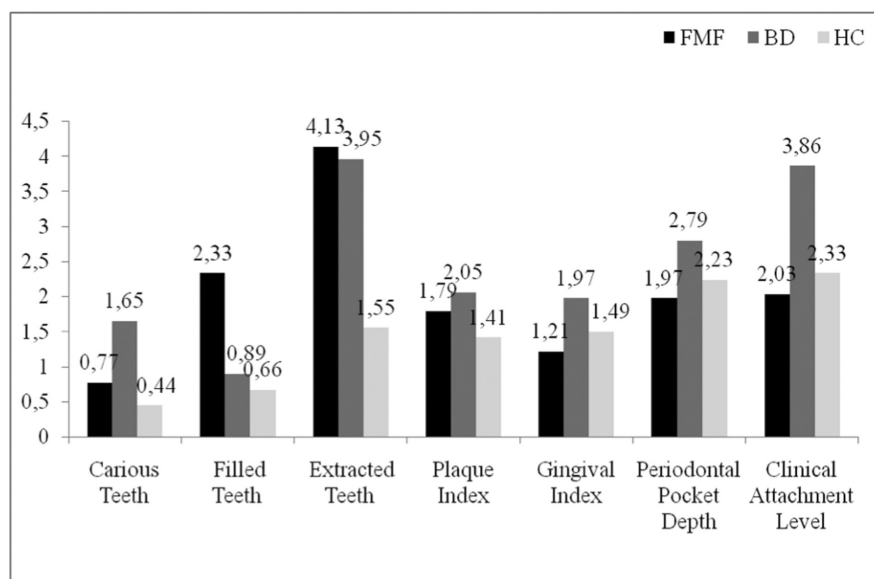Tooth brushing frequency was higher in HC group (2.02±0.84) compared

Fig. 1. Oral health in patients with FMF and controls.

to FMF (1.53±0.85) and BD groups (1.23±0.71) (p<0.0001), whereas it was similar between FMF and BD groups (p=0.782). Tooth brushing frequency was negatively correlated with plaque index (r=-0.36 p=0.01) in FMF group, and with plaque index score and with clinical attachment level (r=0.3, p=0.04 and r=0.4, p=0.017, respectively) in BD group.

Current cigarette smokers were 30% (n=15) in FMF, 48% (n=24) in BD and 44% (n=22) in HC groups. The number of cigarettes smoked per day was similar in HC (4.73±7.92), in BD (4.89±7.19) (p=0.99), and in FMF groups (4.06±7.02) (p=0.713). In HC group, a negative correlation was seen between cigarette consumption and frequency of tooth brushing (r=-0.37, p=0.017).

Quality of Life
OHIP-14 scores, as well as the scores of eight subscales of SF-36 are shown in Table I. OHIP-14 score was significantly higher in FMF and BD groups compared to HC groups (p<0.0001). OHIP-14 score in FMF group was similar to BD group (p=0.294) and correlated with the number of extracted teeth (r=0.38, p=0.010).

Scores of SF-36 subscales regarding "physical functioning", "general health" "bodily pain" and "social functioning" were significantly lower in

FMF group, compared to HC group (p<0.0001; p<0.0001; p<0.0001), whereas the other four subscales were not significantly different (Table I). When we compared FMF and BD groups, "social functioning" subscale was significantly lower (p<0.0001), and "mental health" subscale was significantly higher (p<0.0001) in FMF group. There was no significant difference in the remaining six subscales between FMF and BD groups (Table I).

Discussion
In the present study, we investigated both the oral health status and oral health-related QoL in FMF. For this purpose, we used a comprehensive approach and combined the use of general, as well as oral-specific measures. Among the seven parameters used in this study for evaluating oral health status, only the numbers of extracted teeth and filled teeth were significantly higher in FMF group compared to HC group. OHIP-14 scores reflecting oral health-related QoL were also significantly worse in FMF group compared to HC group. In FMF group, OHIP-14 scores were positively correlated with the number of extracted teeth. Interestingly, none of the parameters were significantly different between FMF subgroups with severe and mild clinical disease severity.

Given that FMF is an autoinflamma-

Table I. Quality of life status in patients with FMF and controls.

	FMF (n=45)		BD (n=50)		HC (n=50)		*p*-value	*p*-value	*p*-value
	Mean	SD	Mean	SD	Mean	SD	FMF-BD	FMF-HC	BD-HC
OHIP-14 Score	24.80	6.92	21.74	13.6	8.54	7.56	0.294	**<0.0001**	**<0.0001**
SF-36 Physical functioning	70.11	26.95	67.7	31.68	90.71	12.45	0.890	**<0.0001**	**<0.0001**
SF-36 Role physical	65.69	36.60	53.5	46.01	81.12	29.1	0.274	0.131	**0.001**
SF-36 General health	49.18	23.37	43.79	21.24	67.76	18.57	0.440	**<0.0001**	**<0.0001**
SF-36 Bodily pain	48.33	6.77	57.43	28.87	71.46	20.89	0.124	**<0.0001**	**0.004**
SF-36 Social functioning	49.12	10.34	67.73	23.02	77.25	21.23	**<0.0001**	**<0.0001**	**<0.0001**
SF-36 Vitality	53.25	20.23	48.1	21.85	55.8	18.88	0.445	0.820	0.146
SF-36 Role emotional	66.61	37.17	56.73	47.9	72.01	38.3	0.399	0.108	0.15
SF-36 Mental health	60.18	19.96	39.12	18.48	52.64	11.35	**<0.0001**	0.08	**<0.0001**

tory disease where innate immune system plays an important role, infectious agents, including potential pathogens in the oral cavity may affect disease course. Poor oral health, caused by focal oral infection foci is well known to be a risk factor for many chronic systemic diseases (10-12). Indeed, poor periodontal health was previously reported even in FMF, but these reports had been confined to FMF patients having amyloidosis resulting with renal failure (30, 31). However, these results could be predicted, as chronic renal disease is already a risk factor for poor oral health (9).

Although from a clinical and pathogenetic point of view, BD is completely different from FMF, in the present study, BD was chosen as the disease control group, simply because of the tendency to impairment in oral health-related QoL. Since oral ulcers are the cardinal clinical symptoms in BD, poor oral health may readily be expected in patients with BD. Consequently, impairment in both general and oral health-related QoL was clearly shown in patients with BD in previous studies (11, 12, 27, 32).

When we compared oral health status and oral health-related QoL in FMF with BD group, in general FMF group seems to be in a better condition. Only the number of filled teeth was significantly higher in FMF group, compared to BD, while OHIP-14 scores were not significantly different between FMF and BD groups. OHIP-14 is the most widely used questionnaire which measures the impact of oral disorders on oral health-related QoL (26). While most of the parameters of oral health

status were better in FMF group compared to BD group, it may be difficult to explain relatively high OHIP-14 scores observed in FMF patients. However, we found a positive correlation between the numbers of extracted teeth and OHIP-14 scores in FMF patients, and it may be speculated that tooth loss might have contributed to impaired oral health-related QoL, *i.e*. higher OHIP-14 scores in FMF patients, as also reported in previous studies (33, 34). In the literature, higher OHIP-14 scores were also reported in some other chronic rheumatic diseases including Sjögren's syndrome (35).

In FMF patients, although the frequency of carious teeth was significantly lower than the BD group, and similar to the HC group, there was still a significant correlation between the number of carious teeth and ESR in FMF group. It is possible that oral infections may possibly contribute to the mildly elevated acute-phase responses observed in FMF, as a marker of subclinical inflammation (36).

SF-36 is a commonly used generic questionnaire and measures the impact of general health condition on QoL (27, 28, 37-39). In the present study, most of the subscales were found to be significantly worse in FMF patients compared with HC group. This is in line with the previous studies reporting impaired general QoL in FMF patients compared to healthy controls (40-43). Disease manifestations such as recurrent attacks and subclinical inflammation (44), as well as overall anxiety and depression (40), might possibly lead to poor general QoL pattern in FMF. Interestingly, in the current study, only "mental health"

subscale in the FMF group was found to be similar to the HC group and significantly better than the BD group.

There are some limitations in our study. Firstly, data regarding MEFV gene mutation analysis were not available for all FMF patients. Secondly, currently smoking patients and smoking controls were not excluded from the study. However, the number of cigarettes smoked per day was similar between the groups, and this also enabled us to observe the actual state of oral health. Thirdly, only FMF patients from the Aegean region and BD patients from the Marmara region were included in the present study. However, we think this sampling is not a major bias, as the socio-economic pattern is very similar in both regions. Finally, all of the FMF patients had been under regular colchicine treatment which controls disease activity effectively in the majority of the patients. Better disease control with colchicine may probably mask the negative effects of impaired oral-health on FMF.

Conclusion
In conclusion, in patients with FMF, oral health-related QoL and some of the parameters of oral health status were found to be worse, compared to HC group. Tooth loss in FMF patients seems to be a critical factor contributing to impaired oral QoL. However, overall oral health status in FMF patients is generally better than in BD patients, suggesting that contribution of oral environment to both disease patterns is different. As an environmental risk factor, oral health status does not seem to be a major determinant of disease activity in FMF.

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