

# Health-related quality of life of school-age children with familial Mediterranean fever

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of life, familial Mediterranean fever,  
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### ABSTRACT

**Objectives.** To describe and compare the parent proxy-reported and child self-reported physical and psychosocial HRQOL of school-age children who have FMF with healthy peers.

**Methods.** The Pediatric Quality of Life Inventory™ 4.0 (PedsQL™ 4.0) Generic Core Scales was used to measure HRQOL. Fifty-one patients and 81 healthy peers were enrolled in the study. Patients were grouped according to their ages as: 1) Children (8 – 12 years) and 2) Adolescents (13 – 18 years). An accompanying parent completed the parent proxy-report of the PedsQL™ 4.0.

**Results.** PedsQL™ scores of children (8-12 years) with FMF were significantly lower than healthy peers for physical and psychosocial functioning for both child self-report and parent proxy-report. The parent proxy-report and child self-reported PedsQL™ scores of adolescent patients (13-18 years) with FMF were lower than the healthy group for physical, emotional, and school functioning; however no significant difference was detected regarding the social functioning. Adolescents with FMF had significantly higher social functioning scores when compared to the younger age group (8-12 years) with FMF,  $92.6 \pm 8.5$  and  $82.2 \pm 17.6$ , respectively ( $p=0.028$ ). The scores of physical, emotional, and school functioning were similar in both groups ( $p=0.73$ ,  $p=0.93$ , and  $p=0.91$ , respectively). Correlations among child self-report subscales and proxy-report subscales were all significant and varied from moderate to high.

**Conclusion.** This study suggested that assessment of HRQOL has potential clinical implications for the healthcare needs of children and adolescents with FMF. Given the degree of reported impairment in their health-related quality

of life, individualized counseling and interventions are needed.

### Introduction

Familial Mediterranean fever (FMF) is the most common inherited autoinflammatory disorder characterized by recurrent episodes of peritonitis, pleuritis, and arthritis, which are usually associated with fever (1). The disease is much more common in individuals of Mediterranean descent than in persons of any other ethnicity. Colchicine therapy has dramatically improved the prognosis of FMF by decreasing the frequency of attacks and preventing amyloidosis, which is the most feared manifestation of the disease (2, 3). On the other hand, there are also concerns about the non-medical problems of FMF patients such as missing school or work days due to attacks or hospital visits, and compliance to a life-long treatment. In this regard, health-related quality of life has become a prominent issue in clinical medicine, health services and outcomes research (4). The World Health Organization defines health-related quality of life (HRQOL) as the individuals' perception of their position in life in the context of the culture and value systems in which they live, and in relation to their goals, expectations, standards, and concerns (5). Studies on HRQOL have improved our point of view in health care by revealing the impact of diseases on physical and psychosocial activities of the patients (6-8). Nevertheless, only a few published studies about FMF have focused on such problems. The impact of disease on health-related quality of life of patients with FMF has been investigated in adults by Buskila *et al.* (9). They found lower HRQOL in FMF patients in comparison to healthy controls. However, the HRQOL in pediatric FMF patients remains unexplored.

Competing interests: none declared.

The aim of this study was to describe and compare the parent proxy-reported and child self-reported physical and psychosocial HRQOL of school-age children who have FMF with healthy peers by using a multidimensional, well validated, and reliable HRQOL instrument. Based on the previous HRQOL literature with other pediatric chronic health conditions (10-12) and the adult HRQOL literature on FMF, we hypothesized that pediatric patients with FMF would report significantly lower overall HRQOL than healthy controls.

## Patients and methods

### Study population

This study was conducted at Dokuz Eylül University Faculty of Medicine, Department of Pediatrics, Division of Immunology and Rheumatology in Izmir, Turkey, between November 2007

and October 2008. Participants included children and adolescents (8 to 18 years old) and their parents. Fifty-one patients (25 males and 26 females) with FMF and 81 healthy controls (44 males and 37 females) were enrolled in the study. The FMF patients fulfilled the Tel-Hashomer criteria (13). MEFV mutations were identified in 44 of 50 patients, of which one patient was not tested. Fourteen patients were homozygous for M694V mutation, and eleven other genotypes were present in the remaining 30 patients. All of the patients were on colchicine treatment. None of the patients in the study had an acute attack at the time of evaluation. The clinical characteristics of the patients are given in Table I. The children in the healthy group were selected from the relatives of health care workers who had no history of chronic disease.

Patients and controls were grouped according to their ages as follows: 1) children (8–12 years), and 2) adolescents (13–18 years). The mean ages of the patients in the child and adolescent groups were  $9.6 \pm 1.7$  yr and  $15.6 \pm 1.8$  yr, respectively and of the controls in child and adolescent groups were  $10 \pm 1.3$  yr and  $16.1 \pm 1.2$  yr, respectively. No significant difference considering age and gender was found between the patients and the controls.

### Methods

The Pediatric Quality of Life Inventory™ 4.0 (PedsQL™ 4.0) Generic Core Scales was the HRQOL instrument used. The study protocol was approved by the ethics committee of the Dokuz Eylül University, Faculty of Medicine. Parents and children were informed about the meaning of HRQOL, the instruments, and the procedure. An accompanying parent, preferably the mother if available, completed the parent proxy-report of the PedsQL™ 4.0. The parent-proxy respondents were mothers (90%) and fathers (10%) in the patient group.

Demographic data, disease duration, FMF symptoms, number of attacks in the last year, number of hospitalizations and/or emergency room visits, disease severity score (14), MEFV mutation, dose of colchicine, and compliance to treatment were recorded for each patient. The disease severity score was calculated according to the scoring system suggested by Pras *et al.* (14). Eleven patients (21%) had mild, 32 (63%) had moderate, and 8 (16%) had severe disease according to this scoring system. The starting dose of colchicine was 0.5 mg/day for children  $\leq 5$  years of age, 1.0 mg/day for children  $> 6$  years of age. Colchicine dose was increased in a stepwise fashion (0.25 or 0.5 mg/step) up to a maximum of 2.0 mg/day to control disease in patients who do not clinically respond to starting dose. Patients were asked if they regularly used colchicine as prescribed and defined as “compliant” if they took the recommended doses. The patients who missed drug doses were defined as “non-compliant”. Nine patients were non-compliant by their statements. The patients with good compliance were

**Table I.** Demographics of FMF patients.

Variable		
Disease duration (years)		
Range		1-12
Mean $\pm$ SD		$3.5 \pm 3.0$
No. of attacks in the last year		
Mean $\pm$ SD		$3.8 \pm 3.1$ (min. 0, max. 15)
Disease severity score (%)		
1		21%
2		63%
3		16%
FMF symptoms (%)		
Fever		82%
Peritonitis		90%
Pleuritis		50%
Arthritis (episodic)		41%
Rash		14%
Orchitis (males)		8%
Myalgia		35%
Arthralgia		39%
Nephropathy/Amyloidosis		0%
Dose of colchicine (mg/day)		$1.2 \pm 0.3$ (min 1, max 2)
Compliance to colchicine treatment (%)		82%
MEFV mutation (n)		
Homozygous	M694V/M694V	14
	M680I/M680I	2
	E148Q/E148Q	1
		1
Compound heterozygous	M694V/M680I	7
	M694V/V726A	4
	M694V/R761H	2
	V726A/M680I	1
	V726A/F479L	1
	E148Q/V726A	1
	E148Q/P369S	2
Heterozygous	M694V	9
	E148Q	1
Not identified		5

grouped according to their response to colchicine. The response was evaluated according to previously suggested principles by Ben-Chetrit and Özdoğan depending on the decrease rate of annual FMF attacks (15). If colchicine reduced the attack rate by 50%, we designated it as “FMF-50” response. Among 42 patients with good compliance 33 patients (78%) achieved FMF-50 response.

*Pediatric Quality of Life Inventory™4.0 (PedsQL™ 4.0)*

The 23-item PedsQL™ 4.0 Generic Core Scales encompass: 1) Physical Functioning (8 items), 2) Emotional Functioning (5 items), 3) Social Functioning (5 items), and 4) School Functioning (5 items), and were developed through focus groups, cognitive interviews, pre-testing, and field testing measurement development protocols (16, 17). The instrument takes approximately 5 minutes to complete. The validity and reliability of Turkish version of PedsQL™ 4.0 Generic Core Scales in children 8–12 years old (unpublished data) and in adolescents 13–18 years old were reported previously (18).

The PedsQL™ 4.0 Generic Core Scales are comprised of parallel child self-report and parent proxy-report formats. Child self-report includes ages 5–7, 8–12, and 13–18 years. Parent proxy-report includes ages 2–4 (toddler), 5–7 (young child), 8–12 (child), and 13–18 (adolescent), and assesses parent’s perceptions of their child’s HRQOL. The items for each of the forms are essentially identical, differing in developmentally appropriate language, or first or third person tense. The instructions ask how much of a problem each item has been during the past one month. A 5-point response scale is utilized across child self-report for ages 8-18 and parent proxy-report (0 = never a problem; 1=almost never a problem; 2 = sometimes a problem; 3 = often a problem; 4 = almost always a problem).

Items are reverse-scored and linearly transformed to a 0-100 scale (0=100, 1=75, 2=50, 3=25, 4=0), so that higher scores indicate better HRQOL. Scale Scores are computed as the sum of the items divided by the number of items

**Table II.** Parent proxy-reported and child self-reported PedsQL™ scores of pediatric patients with FMF and healthy children.

Scale	FMF patients			Healthy controls			p*
	no.	Mean	SD	no.	Mean	SD	
1) Child (8-12 yr)							
<i>Self-report</i>							
Total score	22	72.47	16.68	38	86.29	8.57	0.001
Physical functioning	22	74.31	18.46	38	86.43	8.87	0.022
Psychosocial health	22	69.90	20.14	38	86.27	10.77	0.001
Emotional functioning	22	66.00	25.83	38	81.31	13.73	0.027
Social functioning	22	82.25	17.65	38	94.86	8.25	0.001
School functioning	22	64.00	20.10	38	82.36	14.08	0.001
<i>Proxy-report</i>							
Total score	22	68.55	19.73	38	87.88	9.85	0.000
Physical functioning	22	68.40	23.04	38	86.94	12.05	0.002
Psychosocial health	22	67.92	20.97	38	88.37	9.58	0.000
Emotional functioning	22	66.42	25.45	38	83.94	13.76	0.015
Social functioning	22	77.14	23.74	37	96.44	7.25	0.000
School functioning	22	60.71	24.20	37	84.60	12.75	0.000
2) Adolescent (13-18 yr)							
<i>Self-report</i>							
Total score	29	72.92	14.17	43	82.25	11.23	0.006
Physical functioning	29	70.97	19.16	43	82.49	12.52	0.013
Psychosocial health	29	74.29	12.42	43	91.97	12.58	0.006
Emotional functioning	29	66.78	19.82	43	77.99	15.29	0.022
Social functioning	29	91.39	17.19	42	92.67	8.55	0.261
School functioning	29	65.00	19.19	43	76.62	15.83	0.013
<i>Proxy-report</i>							
Total score	29	72.10	17.10	43	84.59	11.29	0.002
Physical functioning	29	68.01	19.81	43	84.22	12.91	0.001
Psychosocial health	29	76.54	15.96	43	85.98	11.56	0.008
Emotional functioning	29	70.71	23.24	43	82.90	15.66	0.027
Social functioning	28	90.35	11.77	42	93.37	12.42	0.252
School functioning	27	68.21	21.09	42	82.20	14.48	0.006

SD: standard deviation; \*Mann-Whitney U-test.

answered (this accounts for missing data). If more than 50% of the items in the scale are missing, the Scale Score is not computed. The Physical Health Summary Score (8 items) is the same as the Physical Functioning Scale. The Psychosocial Health Summary Score (15 items) is the mean computed as the sum of the items divided by the number of items answered in the Emotional, Social, and School Functioning Scales. The total scale score is the mean of Physical and Psychosocial Health Summary Scores.

*Statistical analysis*

The data were evaluated using the Statistical Package for Social Sciences (SPSS) 11.0 program for Windows and by analyzing descriptive statistics (means, standard deviation), comparing the means of quantitative data for more than two groups with Kruskal-Wallis

test and by comparing dual groups using the Student *t*-test and Mann-Whitney U-test when appropriate. Internal consistency of the scale was determined by calculating Cronbach’s coefficient alpha. Scales with reliabilities of 0.70 or greater are recommended for comparing groups. Intercorrelations were computed through the Pearson’s correlation analysis. A *p*-value ≤0.05 was considered significant.

**Results**

PedsQL™ scores of children (8–12 years) with FMF were significantly lower than healthy peers for physical and psychosocial functioning for both child self-report and parent proxy-report (Table II). The parent proxy-report and child self-reported PedsQL™ scores of adolescent patients (13–18 years) with FMF were lower than the healthy group for physical, emotional,

**Table III.** Intercorrelations of the PedsQL Scale scores between FMF patients and their parents.

		Patient self-report				Parent proxy-report						
		TSS	PFS	PsychoSS	EFS	SFS	SchFS	TSS	PFS	PsychoSS	EFS	SFS
Patient self-report	PFS	0.874**										
	PsychoSS	0.893**	0.577**									
	EFS	0.801**	0.562**	0.854**								
	SFS	0.629**	0.393*	0.721**	0.476**							
Parent proxy-report	SchFS	0.793**	0.546**	0.843**	0.575**	0.514**						
	TSS	0.880**	0.790**	0.769**	0.644**	0.616**	0.731**					
	PFS	0.805**	0.858**	0.571**	0.522**	0.412*	0.560**	0.914**				
	PsychoSS	0.804**	0.586**	0.842**	0.665**	0.759**	0.752**	0.902**	0.659**			
	EFS	0.722**	0.539**	0.761**	0.777*	0.513**	0.584**	0.791**	0.579**	0.866**		
	SFS	0.557**	0.390*	0.606**	0.351*	0.858**	0.518**	0.694**	0.488**	0.817**	0.537**	
	SchFS	0.772**	0.561**	0.787**	0.532**	0.618**	0.825**	0.817**	0.613**	0.880**	0.638**	617**

TSS: total scale score; PFS: physical functioning score; PsychoSS: psychosocial health summary score; EFS: emotional functioning score; SFS: social functioning score; SchFS: school functioning score.

Pearson correlation test (low correlation: 0.10 – 0.29, medium correlation: 0.30 – 0.49, and high correlation  $\geq 0.50$ ).

\* $p < 0.01$ , \*\* $p < 0.001$ .

and school functioning; however no significant difference was detected regarding the social functioning (Table II). Adolescents with FMF had significantly higher social functioning scores when compared to the younger age group (8–12 years) with FMF,  $92.6 \pm 8.5$  and  $82.2 \pm 17.6$ , respectively ( $p = 0.028$ ). The scores of physical, emotional, and school functioning were similar in both groups ( $p = 0.73$ ,  $p = 0.93$ , and  $p = 0.91$ , respectively). The total scale score was not significantly different between male and female patients ( $75.4 \pm 13.9$  vs.  $70.3 \pm 15.7$ ,  $p = 0.22$ ).

There was no significant correlation between the total scale score and disease duration ( $r = 0.13$ ,  $p = 0.35$ ). There was a negative correlation between total scale score and FMF severity score ( $r = -0.40$ ,  $p = 0.003$ ). The FMF-50 responders had significantly higher total scale scores than the others ( $76.5 \pm 13.3$  vs.  $58.9 \pm 14.1$ ,  $p = 0.002$ ). The total scale score was inversely correlated with the number of attacks ( $r = -0.571$ ,  $p = 0.000$ ) as well as number of hospitalizations and/or emergency room visits ( $r = -0.44$ ,  $p = 0.001$ ). The patients who were non-compliant to colchicine had significantly lower total scale scores than the compliant group ( $76.5 \pm 12.6$  vs.  $58.3 \pm 13.7$ ,  $p = 0.002$ ). The total scale score was significantly lower in patients with myalgia than the patients without myalgia ( $63.9 \pm 9.4$  vs.  $75.9 \pm 15.5$ ,  $p = 0.005$ ). The total scale

score was significantly lower in patients with arthralgia than the patients without arthralgia ( $64.2 \pm 11.1$  vs.  $76.6 \pm 15.1$ ,  $p = 0.005$ ). The patients with myalgia had significantly lower physical functioning scores than the patients without myalgia,  $60.3 \pm 13.4$  vs.  $76.6 \pm 18.6$  ( $p = 0.004$ ). Similarly, patients with arthralgia had significantly lower physical functioning scores than the ones without arthralgia,  $59.9 \pm 11.6$  vs.  $77.9 \pm 18.7$  ( $p = 0.001$ ). Regarding that the most prevalent genotype of FMF in this study was M694V/M694V; patients having this mutation were compared to patients having other genotypes. The physical and psychosocial scale scores of the patients homozygous for M694V were not significantly different from the others ( $p = 0.92$  and  $p = 0.89$ , respectively).

Correlations among child self-report subscales and proxy-report subscales were all significant and varied from moderate to high (Table III). Internal consistency reliability alpha coefficients for self-reports of patients and controls were 0.77 and 0.87, respectively. Internal consistency reliability alpha coefficients for parent proxy-reports of patients and controls were 0.80 and 0.89, respectively. They all exceeded the minimum reliability standard of 0.70.

### Discussion

The health-related quality of life of pediatric patients with rheumatic dis-

eases has been recognized as an important factor in the assessment of health as well as in planning treatment and management strategies (10–12). Previously, adult patients with FMF were shown to have impaired HRQOL (9). Additionally, Press *et al.* reported that the HRQOL of parents living with a child with FMF was also impaired when compared to parents of healthy children (19). This is the first study describing the health-related quality of life of patients with FMF in a pediatric population.

The patient group aged 8–12 years reported significantly lower scores on all dimensions of the PedsQL™ (physical, emotional, social, and school functioning) in comparison to healthy children. However, the self-reported and parent proxy-reported social functioning scores of adolescent patients were not different from the healthy peers, while the physical, emotional, and school functioning scores were lower. Social functioning scale assesses peer relationships. The results suggested that FMF patients in the 8–12 years group have more difficulties with peer relationships than adolescent patient group.

It is worthy to note that school functioning seems to be the most affected HRQOL dimension for both FMF patient age groups. The PedsQL™ School Functioning Scale assesses children's ability to concentrate and keep up with school work, and the amount of school



missed due to the illness and its treatment. Missing school days due to attacks or doctor visits might be some of the reasons for the school functioning impairment in this study. However, to date, no data have been reported about the cognitive functioning of pediatric patients with FMF. Therefore, further studies are required to investigate if there is cognitive dysfunction in pediatric patients with FMF resulting in impaired school functioning.

This study demonstrated that the HRQOL of pediatric FMF patients is negatively affected from disease severity scores and number of attacks. Buskila *et al.* (9) also showed an inverse correlation between QOL scores and number of attacks in adult FMF patients. In addition, we found lower HRQOL scores in non-compliant patients. Poor compliance may increase attack rate of FMF. Besides, it is worthy to note that compliance is often a marker of patients' and parents' understanding and adaptation to a chronic disease, which may be a result rather than a cause for lower HRQOL.

FMF is a disease that might rarely cause debilitating physical effects such as chronic arthritis and amyloid nephropathy, which would definitely affect the HRQOL of these patients (3). The significantly impaired physical functioning scores in both age groups in this study were striking, despite the fact that none of the patients had chronic arthritis or amyloid nephropathy. These pediatric patients had myalgia or arthralgia lasting for a few hours to whole day, mainly affecting the legs following a physical exertion or even prolonged standing (20). Higher frequencies of arthralgia and myalgia have been reported in the Turkish population in comparison to Arab and Jewish populations (20-22). A pediatric series reported by Ertekin *et al.* (23) revealed that 55.8% and 26.2% of Turkish children with FMF had arthralgia and myalgia, respectively. In a nationwide multicenter study (24), the rate of myalgia was 39.6%. In the study of Buskila *et al.* (9), the HRQOL of adult FMF patients was shown to be inversely correlated with the diffuse widespread pain associated with fibromyalgia syndrome. The frequency

of arthralgia and myalgia in this study (39% and 35%, respectively) was in concordance with the others. The results in this study showed that muscle and joint pain, the common manifestations of FMF, could themselves impair HRQOL in these pediatric patients.

While pediatric patient self-report should be considered as the standard for measuring perceived HRQOL, it is typically parents' perceptions of their children's HRQOL that influences health-care utilization. In several studies, an imperfect agreement exists between parent proxy- and pediatric patient self-reports (25, 26). In this study, a good agreement between self-reports and proxy-reports was documented, which increased the strength of the results.

The strengths of this study include the use of reports from both parents and children obtained using the PedsQL™, a pediatric HRQOL instrument with previously demonstrated reliability and validity in pediatric rheumatic diseases (10-12). Limitations include the small sample size and the inclusion of children who were all attending the same rheumatology clinic, which may limit the geographic, racial, and ethnic diversity of the sample. As a result it is necessary to be cautious when generalizing the results of this study to all children with FMF.

In conclusion, this study suggested that assessment of health-related quality of life has potential clinical implications for the healthcare needs of children and adolescents with FMF. Given the degree of reported impairment in their health-related quality of life, individualized counselling and interventions are needed.

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