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Original Article

Serum Uric Acid Level Among Children with Familial Mediterranean Fever

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Abstract:
Background: Familial Mediterranean fever (FMF) is the most frequent form of inherited periodic fever syndromes. It is caused by a mutation in the MEFV gene and is transmitted by autosomal recessive mode. It is marked by recurring fever episodes with a range of symptoms due to inflammation in the pleura, synovium, and peritoneum. In FMF patients, subclinical inflammation frequently persists throughout the attack-free periods. Uric acid is a product of purine nucleotides catabolism. It is elevated in tissue damage.
Aim of the work: To assess uric acid levels and glomerular filtration rate (GFR) in children with FMF during the attack-free period.
Subjects and Methods: This cross-sectional study assessed uric acid levels and GFR in 40 children with FMF during the attack-free period. They were enrolled from the Pediatric Rheumatology Outpatient Clinic, Children's Hospital, Faculty of Medicine, Cairo University. Their uric acid levels were compared to a control group of 40 healthy age and sex-matched children.
Results: The mean ± SD age of FMF patients was 12.65 ± 1.82 years and 50% were males while the control group mean age was 12.6 ±1.82 years (p=0.903) and 52.5% were males (p=0.823). The mean± SD GFR among FMF patients was 124.75 ± 43.91(ml/min/1.73m²), while among the control group it was 155.48 ± 63.17 ml/min/1.73m² (p =0.054). Seven (17.5%) FMF patients had reduced GFR (mean ± SD = 84.29± 3.15 ml/min/1.73m²). The mean ± SD uric acid folds of upper level of normal was 0.55 ± 0.13 among the control group, 0.75±0.21in the FMF group, 0.49 ± 0.21 among those with normal GFR and 0.74 ± 0.21 among those with reduced GFR respectively (p=0.286). Three (7.5%) of the FMF patients had microalbuminuria and normal GFR.
Conclusion: Uric acid levels were within normal range for age among children with FMF during the attack-free periods and were not predicative of impaired GFR or presence of albuminuria. In a subset of FMF patients, GFR was impaired and others had microalbuminuria during the attack-free periods despite having normal kidney functions. More studies are needed to highlight the risk factors and value of GFR and microalbuminuria in follow up of children with FMF. SUA levels were not elevated in children with FMF during the attack-free period.

Level of Evidence of Study: IV (*1*)**.**
Keywords: Colchicine; Familial Mediterranean Fever; GFR; uric acid; attack-free periods
Abbreviations: BMI: Body mass index; CKD: Chronic kidney disease; FMF: Familial Mediterranean Fever; GFR: Glomerular filtration rate; MEFV: Mediterranean Fever; SAA: Serum amyloid A; SUA: Serum uric acid

Introduction

Familial Mediterranean fever (FMF) is the most common monogenic autoinflammatory illness (*2*). Repeated inflammatory episodes of fever and serositis are the hallmarks of this condition (*3*), usually childhood-onset, with a notably higher incidence among people with Middle Eastern and Mediterranean ancestry (*4*). The FMF causative gene has ten exons and produces the 781 amino acid protein pyrin, is found on the short arm of chromosome 16 (16p13.3) (*5*). Amyloidosis is a devastating complication of FMF (*2*), associated with increase in serum amyloid A (SAA) production (*6*). Amyloidosis A typically presents as a nephrotic syndrome with a rapid progression to end-stage kidney disease (*7*). The non-amyloid kidney disease in FMF patients includes mesangial IgA nephropathy, crescentic, rapidly progressing glomerulonephritis, diffuse proliferative glomerulonephritis, IgM nephropathy, and vasculitis. They are mainly related to the uncontrolled inflammation (*8*). Inflammation also plays an important role in the pathogenesis of

CKD. Circulating pro-inflammatory cytokines stimulate endothelial and leukocyte cells in the kidney, which disrupt the renal endothelial structure and activate the coagulation system (*9*).

Hyperuricemia is a chronic purine metabolic disorder mainly because of excessive production of uric acid and decreased renal excretion (*10*). Serum uric acid (SUA) level in children is related to age and sex. There are no universally accepted clinical diagnostic criteria for hyperuricemia in children. Boys have higher uric acid levels during adolescence than similar aged girls due to lower estrogen levels, increased body mass index (BMI), and declined fractional urate excretion (*11*). Evidence shows that high serum uric acid contributes directly to glomerular affection in patients with CKD, and correction of hyperuricemia will slow the progression of chronic renal failure in patients with CKD (*12*). Colchicine is the mainstay of treatment of FMF due to its proven efficacy in the prevention of attacks and amyloidosis, even in nonresponsive patients in terms of occurrence of attacks (*13*). Hence, we aimed to assess uric acid levels and glomerular filtration rate (GFR) in children with FMF during the attack-free period.

Subjects and Methods

This cross-sectional study was conducted at the Pediatric Rheumatology Outpatient Clinic, Children's Hospital, Faculty of Medicine, Cairo University. The study was approved by the Ethical Committee of the Faculty of Medicine, Cairo University, Egypt, approved the study (MS-417-2020). All study participants' caregivers, were informed about the goals, procedures, and possible advantages of the research. The participants were enrolled after getting the informed consent of their caretakers.

Participants

A total of 40 patients with known FMF under the age of 17 years who followed up in the Pediatric Rheumatology Clinic were included in this study, all FMF patients were during the attack-free period. Another 40 age and sex-matched healthy children were enrolled in the study as the control group. The FMF patients enrolled in this study had been diagnosed with FMF according to the new pediatric criteria of Yalcinkaya et al. (*14*). Their gene mutations were already documented in their files, and were during the attack-free period (minimum two weeks after the end of the last FMF attack according to clinical and physical assessment). Patients with FMF who suffered from concurrent illness, or infection were ineligible to participate in this study.

Methods

Detailed history taking including demographic data, clinical manifestations during illness course, age of onset of FMF, age at diagnosis, disease duration, number of attacks in last 6 months, dose of colchicine in micrograms, duration of colchicine usage in years and compliance to colchicine were obtained. Assessment of response to colchicine according to FMF 50 score (17) and assessment of FMF severity by the international severity scoring system for FMF (ISSF) (18) were done. They underwent complete general and systemic examinations. Anthropometric measurements, including height (cm), and body mass index (BMI = weight / [height (m)^2] *a*nd waist circumference, were obtained, following the recommendations of the World Health Organization (WHO) and expressed as percentiles according to national normal expected values for age and sex (*15*).

Laboratory investigations included complete blood picture, ESR, BUN, serum creatinine, urine analysis, urinary microalbumin, and serum uric acid levels at the time of the study; Uric acid level was assayed by Cobas: Roche Diagnostics GmbHD-68298, Mannheim, Germany. Serum amyloid A was done for FMF patients only. Hyperuricemia among the participants was based upon the cutoffs of Mayo Clinic Laboratories reference value according to age and sex (the normal upper level ranges between 4.9-7.4 mg/dL according to age and sex). Accordingly it was calculated in folds of upper level of normal for age and sex for each child in both groups (*16*).

Urinary albumin level was measured using the turbidimetric immunoassay method, and patients were instructed to avoid exercise before sample collection. Microalbuminuria was defined as loss of albumin in urine in the range of 30- <300 mg/24 hours.

GFR was assessed using the pediatric eGFR calculator (Creatinine-based bedside Schwartz equation 2009) (*17*). Types of MEFV gene mutations were collected from patients' files.

Statistical Analysis

A computer-assisted statistical analysis was done on the data using SPSS (Statistical Package for Social Science, IBM Corporation, USA), version 22. A chi-square was used to compare categorical variables presented as frequency and percentage. The t-test was used to compare continuous variables reported as mean ± standard deviation. Non-parametric data were compared using the Mann-Whitney-U test and mentioned as the median and interquartile range. Person correlation was used to evaluate the association between continuous variables. P-values below 0.05 were considered as significant.

Results

Disease criteria of the FMF patients group were included in Table 1. 33 (82.5%) of FMF patients had a positive family history of FMF. The mean± SD of disease onset was 4.86 ± 3.57 years; the mean ±SD age at diagnosis was 6.54± 3.54 years, while the mean± SD of disease duration was 7.51± 3.40 years. The most common manifestations throughout the disease course were abdominal pain 11(27%) followed by chest pain 9 (22.5%), fever 7 (17.5%), arthralgia 7 (17.5%) then arthritis 1 (2.5%). Among males with FMF, only 1 (5%) patient had a history of scrotal pain along the disease course. Heterozygous genotypes were present among 31 (77.5%) children with FMF, while homozygous genotypes were found among 6 (15%), and compound heterozygous genotypes in 3 (7.5%). V726A and M694I MEFV gene mutations were the most frequent mutations, representing 17.5% and 15% of cases, respectively. 11 (27.5%) of FMF patients had mild ISSF severity scores, 18 (45%) had intermediate scores, while 11 (27.5%) had severe scores. Among all FMF patients, 25 (62.5%) had a good response to colchicine according to the FMF 50 score.

Demographic data, clinical and laboratory findings of FMF patients, and the control groups are displayed in Table 1. Both groups were age and sex matched. The mean ±SD age of the FMF patients was 12.65 ± 1.82 years, 20 (50%) were females, and 20 (50%) were males, while the mean ± SD age of the control group was 12.60 ± 1.82 years. 19 (47.5%) were females, while 21 (52.2%) were males (p=0.903) and (p=0.823) respectively.

Table 1. The clinical characteristics of the studied FMF patients

	Total cases Number= 40	
	Mean ± SD	Range
Age (years)	12.65 ± 1.82	10-17
Age at disease onset (years)	4.86 ± 3.57	0.1 -11
Age at diagnosis (years)	6.54 ± 3.54	1-14
Disease duration (years)	7.51± 3.40	2-15
Colchicine dose (mic/day)	1243.75 ± 406.23	500-2000
Colchicine usage duration (years)	4.6 ± 3.14	1-14
ISSF score	3.62 ± 1.92	1-6
SAA	82.78± 50.68	1.79 -191
GFR (ml/min/1.73m²)	124.75 ± 34.91	80-221
Urinary Microalbumin (mg/24hours)	13.71 ±15.22	2.6 -92.6
	Number	%
MEFV gene mutation		
Homozygous	6	15
Heterozygous	31	77.5
Compound heterozygous	3	7.5
Compliance to Colchicine		
Compliant	24	60
Non-compliant	16	40
Response to Colchicine		
Good	25	62.5
Poor	15	37.5

GFR: glomerular filtration rate; ISSF International severity score for FMF; MEFV Mediterranean Fever; SAA: serum amyloid A

Our study identified statistically significant differences between FMF patients and the control group regarding height, which was higher in the control group with a (p= 0.024).

Meanwhile, BMI Z-score, systolic, and diastolic blood pressure did not differ between FMF patients and the control group (p=0.085), (p=0.8) and (p=0.814) respectively.

Table 2. Clinical and laboratory findings of FMF patients and control group

	FMF patient group (n= 40)		**Control group (n= 40)**		**P value**
Age (years)					
Mean ± SD	12.65 ± 1.82		12.6 ± 1.82		0.903
Range	10-17		10-16		
	Number	%	Number	%	
Sex					
Females	20	50	19	47.5	0.823
Males	20	50	21	52.5	
Height Percentiles					
Below 3rd percentile	3	7.5	1	2.5	
Between 3rd &10th percentile	1	2.5	0	0.00	
Between 10th & 50th percentile	6	15	6	15	0.024
Between 50th and 90th percentile	22	55	13	32.5	
Between 90th and 97th percentile	7	17.5	9	22.5	
Above 97th percentile	1	2.5	11	27.5	
BMIZ-score (%)					
Between 0 and 1	12	30	20	50	
Between 1 and 2	11	27.5	15	37.5	
Between 2 and 3	5	12.5	2	5	0.085
Below-3	1	2.5	0	0.00	
Between-2 and -1	1	2.5	0	0.00	
Between -1 and 0	10	25	3	7.5	
SBP (mmHg)					
Mean ± SD	106.5 ±11.72		107.13 ±10.18		0.800
Range	80-120		90-120		
DBP (mmHg)					
Mean ± SD	68.50±7.18		68.13 ±7.04		0.814
Range	50-80		60-80		
WBC (x10^3/mm)					
Mean ± SD	7.25 ± 2.34		6.87 ± 2.26		0.458
Range	3.2-15.4		4-14		
Hemoglobin (g/dl)					
Mean ± SD	12.13 ± 0.87		11.98 ± 1.17		0.532
Range	10.5-14.1		8.9-14		
Platelets (x10^3/mm)					
Mean ±SD	310.1 ± 99.68		272.13±83.4		0.068
Range	179-630		135-476		
ESR (mm/1ST h)					
Mean ± SD	14.5		10		0.04
Range	9-24		6-15		
BUN (mg/dl)					
Mean ± SD	13.32 ± 3.8		11.85 ± 4.52		0.146
Range	6-19		5-24		
Creatinine (mg/dl)					
Mean ± SD	0.55 ± 0.15		0.47 ± 0.1		0.018
Range	0.28-0.9		0.2-0.8		
Uric acid (upper fold of normal)					
Mean ± SD	0.75± 0.21		0.55 ± 0.13		0.000
Range	0.37-1.1		0.37-0.89		
GFR (ml/min/1.73m^2)					
Mean ± SD	124.75 ±34.91		155.38 ± 63.28		0.057
Range	80.00- 221.0		86-345		

BMI: body mass index; DBP: diastolic blood pressure; GFR: glomerular filtration rate; SBP: systolic blood pressure

The mean± SD GFR among FMF patients was 124.75 ± 43.91 ml/min/1.73m², while among the control group it was155.48 ± 63.17 ml/min/1.73m² (p =0.054). Seven (17.5%) FMF patients had reduced GFR with mean ± SD 84.29± 3.15 ml/min/1.73m² (range 80-89 ml/min/1.73m²). Yet there were no statistically significant differences between FMF patients with normal and those with impaired GFR as regards age (p= 0.972), sex (p= 0.407), age at disease onset (p=0.917), disease duration (p= 0.889), disease severity scores (p= 0.702), the daily dose of colchicine (p= 0.862), duration of colchicine usage (p= 0.889), FMF 50 score (p= 0.691), SAA levels (p= 0.326), SUA levels (p= 0.626) or urinary albumin/creatinine ratio (p= 0.577).

The mean ± SD folds of upper level of uric acid level among FMF patients was 0.75± 0.21, while in the control group, it was 0.55 ± 0.13 (p=0.0001). Marginal hyperuricemia was detected among 2 (5%) of FMF patients (1.1 upper folds of normal). Both had normal GFR. ESR was higher in FMF patients than in the control group (p=0.04).

Microalbuminuria with normal GFR was detected in 3 (7.5%) of the FMF patients 35, 36.9 and 92.6 mg/day; there were no correlations between microalbuminuria with age of patients (p=0.249), age of onset (p=0.06), age at diagnosis (p=0.349), disease duration (p=0.06), disease severity (p=0.602), or SAA level (p=0.341). There were no differences between FMF patients with normal SUA and those with high SUA regarding age (p=0.261), BMI -z score (p=0.924), disease duration (p=0.741), dose of colchicine (p=0.702), duration of colchicine intake (p=0.972), or response to colchicine (p=0.691).

As shown in Table 2, there was no correlation between serum uric acid levels or GFR with age of onset of FMF (p=0.635), age at diagnosis (p=0.219), disease duration (p=0.731), ISSF score (p=0.127), dose (p=0.987), and duration of colchicine intake (p=0.127), response to colchicine (p=0.868), SBP (p=0.363), DBP (p=0.385), or BUN (p=0.769).

Table 3. Correlation between serum uric acid level and GFR with FMF disease criteria

	Serum uric acid		**GFR**	
	r	**P value**	**r**	**P value**
Age of FMF onset (years)	- 0.077	0.635	0.133	0.412
Age of FMF diagnosis (years)	- 0.199	0.219	- 0.011	0.949
FMF disease duration (years)	0.054	0.741	-0.177	0.273
ISSF severity score	0.022	0.127	-0.287	0.072
Dose of colchicine (microgram/day)	- 0.003	0.987	-0.072	0.661
Duration of colchicine dose (years)	0.245	0.127	-0.118	0.467
BUN (mg/dl)	-0.048	0.769	-0.208	0.197
Creatinine (mg/dl)	-0.224	0.169	-0.934	<0.001

BUN: blood urea nitrogen; FMF: Familial Mediterranean Fever; ISSF: International severity score for FMF

Discussion

Renal amyloidosis is a critical life threatening complication in the natural course of FMF. Early detection of renal involvement is crucial to prevent and control renal amyloidosis. Previous research conducted on adults demonstrated a correlation between uric acid levels and kidney function, it demonstrated a decline in GFR over time was higher in patients with elevated SUA levels (*18*).The current study detected trivial elevation of level of uric acid in only 5% of the studied children with FMF during the attack-free period. There was no elevation in uric acid among the majority of the cases, only 2 (5%) had marginal increase in uric acid levels for age and sex. We did not observe any correlations between serum uric acid level during the attack-free period and different disease characteristics such as age of onset of disease, disease duration, different clinical manifestations, disease severity score, dose of colchicine, and different laboratory investigations, including serum amyloid A. The lack of hyperuricemia during the attack-free period might reflect a regular load of tissue turnover and real control of underlying inflammation and serositis. Hyperuricemia among adult patients with FMF was reported during and in between the attacks (*19*). To our knowledge, no studies discussed the correlation between serum uric acid levels with different FMF disease criteria and different laboratory parameters in children with FMF.

The literature regarding the role of uric acid in FMF is scarce. In one study, there was no statistically significant difference in serum uric acid levels between FMF patients with and without an attack, even though uric acid levels were higher in patients with FMF than in healthy controls (*19*). Another study that compared serum uric acid levels in pediatric FMF patients during the attack period and FMF patients during the attack-free period showed that serum uric

acid levels were higher during the attack period (*20*). Previous research in adults found that SUA levels were higher in FMF patients with metabolic syndrome (*21*); in contrast, our study did not find a correlation between SUA levels and BMI Z score among children with FMF. No difference was detected between both sexes regarding SUA levels among FMF patients, in contrast to previous studies that found SUA lower among girls (*22*). No correlation was detected between SUA level with SBP and DBP, which is similar to others who did not find a relation between SUA levels and hypertension in children with CKD (*23*); this may be related to growth and hormonal changes during puberty.

Microalbuminuria in FMF suggests probable glomerular basement membrane damage and is an important and sensitive marker of early glomerular disease; microalbuminuria was detected in 3 (7.5%) of our FMF patients, their ages were 10, 12, and 14 years old, and the disease duration for all of them was below 5 years which is similar to other studies that detected microalbuminuria in very young children and early during the disease course (*24*). The detected microalbuminuria among them needs to be studied prospectively. We did not collect more than a sample, hence we cannot exclude that microalbuminuria was related to exercise or any mild degree of dehydration, or a real predictor of renal involvement.

Mild decrease in estimated GFR was encountered in 7 (17.5%) of our studied cohort. Yet, we did not study measured GFR among them as it was beyond the scope of this study. We did not repeat the GFR 3 months later, hence they do not fulfill the definition of grade 2 chronic kidney disease (*25*). It is crucial to follow up these children with decreased estimated GFR, repeat the GFR and validate the estimated GFR by inulin measured GFR. There was no microalbuminuria among them and there was no correlation with serum amyloid or any of the other studied parameters. Further prospective follow up will shed light on the outcome of these children and whether they have kidney affection or not.

Given the considerable number of consanguineous marriages in Egypt, it is not surprising that 82.5% of cases had a family history of FMF; a different Egyptian study found that 61% of patients had a family history of FMF (*26*). Of our FMF patients, 17.5% had V726A mutations, and 15% had M694I mutations. We did not find attributes or correlation of type of mutation with microalbuminuria or renal involvement. Yet, the small sample size and cross-sectional study design do not allow drawing any conclusions about the genetic susceptibility of renal involvement in patients having the said mutations.

Our study noted that ESR was slightly higher in FMF patients during the attack-free period than in the control group, it might indicate subclinical inflammation. It was reported in the literature that ESR values do not revert to normal in two-thirds of FMF patients during the attack-free period (*27*). Prospective studies are necessary to outline if this dictates a change of management. Persistent subclinical inflammation increases FMF complications, mainly amyloidosis, which affects GFR. So, the periodic evaluation of SAA titers has a central role in managing FMF.

Progressive renal impairment is a crucial point in the natural course of FMF, so a multidisciplinary approach is required for prevention, early detection, proper follow-up of the state of inflammation and possible complications. In cases of significant microalbuminuria, a complete renal function evaluation must be carried out through measurement of GFR, 24-hour urinary proteins, electrolytes, and serum protein electrophoresis (*28*).

Uric acid and inflammation have previously been discussed, yet more studies are needed to verify how both relate to FMF (*29*), and to subclinical inflammation during the attack-free period.

Our research has many limitations, mainly the limited number of FMF patients and the fact that we did not incorporate patients during the attack period in this study. Also, we calculated the eGFR based on the Schwartz formula, which is influenced by muscle mass, diet, and exercise. We did not compare the GFR estimated by the Schwartz formula to other estimations using cystatin C or the highly accurate yet more invasive inulin (*30*). We were not able to study compliance of patients to colchicine or its correlation to GFR and FMF disease parameters due to lack of a validated objective instrument/questionnaire in Arabic applicable for use with Egyptian children and their caregivers.

Conclusion

Uric acid levels were within normal range for age among children with FMF during the attack-free periods and were not associated with impaired GFR or albuminuria. In a subset of FMF patients, GFR was impaired and others had microalbuminuria during the attack-free periods despite having normal kidney functions. More studies are needed to highlight the risk factors and value of GFR and microalbuminuria in follow up of children with FMF. SUA levels were not elevated in children with FMF during the attack-free period.

Author Contributions:

All authors contributed to the study conception, design and draft. All approved final submitted manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest in connection with the reported study. Authors declare veracity of information.

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