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FMF and Osteoporosis

Increased risk of osteoporosis and femoral neck fractures in patients with Familial Mediterranean Fever - a large retrospective cohort study

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Key Points

1. Familial Mediterranean Fever (FMF) significantly increases the risk of osteoporosis and femoral neck fractures.

2. FMF patients develop osteoporosis at a younger age compared to the general population.

3. Routine monitoring of bone mineral density in FMF patients could help in early detection and prevention of osteoporosis and related fractures.

Abstract

Background: The direct impact of inflammatory conditions and their therapy with corticosteroids both contribute to an increased risk of osteoporosis with associated fractures. Familial-Mediterranean-Fever (FMF) is an autoinflammatory disorder not commonly treated with corticosteroids. Evidence regarding FMF association with osteoporosis and femur fractures is anecdotal.

Objectives: To evaluate the incidence and risk of osteoporosis and femoral neck fracture in FMF patients compared to the general population.

Methods: A retrospective cohort study using the electronic database of Clalit Health Services of all FMF patients first diagnosed between 2000-2016 and controls was evaluated including age and sex matched controls in 1:1 ratio. Follow-up continued until the first diagnosis of osteoporosis or fracture. Risk for these conditions was compared using univariate and multivariate cox-regression models.

Results: 9,769 FMF patients were followed for a median period of 12.5 years. 304 FMF patients were diagnosed with osteoporosis compared to 191 controls, resulting in an incidence rate (per 10,000 persons-years) of 28.8 and 17.8 respectively, and a crude HR of 1.62 (95%CI 1.35 to 1.93; $p<0.001$). Patients were diagnosed with osteoporosis at a considerably younger age than controls (60.1±12.4 vs 62.5±11.0 years; $p=0.028$). 56 FMF patients were diagnosed with femoral neck fracture compared to 35 controls, resulting in an incidence rate of 5.3 and 3.3 respectively, and a crude HR of 1.60 (95%CI 1.05 to 2.44; $p<0.05$).

Conclusion: FMF patients are at increased risk for osteoporosis and consequently femur fracture. Our findings emphasize the importance of considering bone health in the management of FMF patients.

Introduction

Osteoporosis is a common metabolic bone disorder characterized by a reduction in bone mineral density and microarchitectural degradation, with an estimation of up to 50% of patients aged over 50 years being susceptible to osteoporosis-related fractures (1,2). Hip fractures, a major complication of osteoporosis, poses a significant public health concern in elderly individuals and is associated with severe morbidity and mortality (3). Unfortunately, the burden of hip fractures is expected to increase significantly in the coming years due to the aging population and increasing life expectancy (4). Given the substantial impact of osteoporosis on both the population and the economy, numerous efforts are being made to advance risk stratification in an attempt to ensure effective surveillance and prevention (5). Risk factors for osteoporosis are numerous and include advanced age, female gender, low body weight, smoking, excessive alcohol consumption, sedentary lifestyle, and genetic predisposition. Additionally, certain medical conditions such as hyperthyroidism and several inflammatory disorders are associated with osteoporosis. The prolonged use of glucocorticoids including their use for the aforementioned inflammatory disorders can also increase osteoporosis risk (6). The association between osteoporosis and inflammatory states, including chronic autoimmune diseases such as SLE (systemic lupus erythematosus) and RA (rheumatoid arthritis) is well established (7,8). Proinflammatory cytokines play a key role in bone resorption and osteoclastogenesis process (9).

Familial Mediterranean Fever (FMF) is an inherited, chronic, auto-inflammatory disorder characterized by recurrent episodes of fever, arthritis and serositis, such as peritonitis and pleuritis. The genetic etiology of FMF is a mutation in the MEFV gene, which encodes for the pyrin protein. FMF is primarily found in people of Mediterranean ancestry, including non-Ashkenazi Jews, Turks, Armenians and Arabs. Progression of

FMF may result in distressing outcomes including renal failure, amyloidosis, and even mortality (10,11). Studies exploring the link between osteoporosis and autoinflammatory diseases such as FMF are scarce, with inconclusive results and without any association with fractures, however limited by small cohorts not representative of the general population (12–15). Furthermore, unlike many other autoimmune disorders, FMF patients typically do not receive steroid treatments (10). This removes a significant secondary risk factor for osteoporosis development, ensuring that any diagnosed osteoporosis is more directly linked to the disease's inflammatory status rather than treatment side effects.

Given the scarcity of evidence and the importance of utilizing both risk stratification and preventive measures in the management of osteoporosis, we examined the risk of osteoporosis in general, and specifically femoral neck fracture, among FMF patients in large-scale retrospective population-based cohort.

Material and Methods

Ethics

The present study received ethical approval from the Clalit Health Services (CHS) Ethical Committee, situated in Beer-Sheva, Israel. The study was exempted from obtaining informed consent due to its retrospective nature.

Design and Study Population

This study was designed as a retrospective cohort study drawing data from the established CHS integrated electronic health records database. CHS is the largest health organization in Israel which operates in a payer-provider model providing services to

more than half the population in Israel. CHS maintains a completely digitalized integrated health record drawing data continuously from a network of in-house and external primary care clinics, hospitals, pharmacies, laboratories and imaging institutes. This database has been used extensively in respected peer-reviewed journals (16,17), including studies specifically addressing FMF patients (18–20).

Our study cohort included all FMF patients first diagnosed from January 2000 to December 2016. Each FMF patient was matched with one control without a diagnosis of FMF, based on date of birth, sex, place of residency, and index date (that was set to be the same as the date of diagnosis for their corresponding FMF patients). Follow up from first FMF diagnosis continued until the date of the diagnosis of osteoporosis or femoral neck fracture (defined as an event), death, or end of follow up (censored cases). Patients with a diagnosis of osteoporosis or femoral neck fracture before the beginning of follow-up were excluded from the analysis.

Study variables

Socioeconomic status was derived from the CHS area specific codes in accordance with the neighborhood level and was further split up into three groups based on national census data. Ethnic origin was derived from country of birth data and then further allocated into geographic regions. Diagnosis of osteoporosis and femoral neck fracture, as well as other chronic comorbidities including obesity, diabetes, thyroid and parathyroid disorders, SLE, RA and sarcoidosis were based on the CHS chronic diseases registry, which has shown to have high accuracy in validation studies (21). Smoking was included on a never/ever basis at the start of follow-up. Complications of FMF, including chronic renal failure and amyloidosis were identified in a similar manner. Colchicine treatment was derived from drug prescriptions and duration of

treatment was extrapolated from the first and last prescriptions for a particular subject during the study follow-up.

Statistical analysis

Continuous variables are registered as mean +/- standard deviation. Standard t-test is used for comparisons. Categorical variables are registered as percentages, utilizing Pearson's chi-square test for comparisons. The cox-proportional hazard regression model evaluated the risk for osteoporosis and femoral neck fractures among FMF subjects compared to controls and reported as hazard ratio (HR). The statistical analyses were used of an initial crude unadjusted model, then an age-and-sex adjusted model and lastly a fully adjusted model for age, sex, demographics and comorbidities. Predictors of osteoporosis or femoral neck fracture within the FMF cohort were evaluated using a binary logistic regression model and regarded as odds ratio (OR). All p-values were two-tailed, and the null hypothesis was considered valid if $p \geq 0.05$. All statistical analysis were conducted by using SPSS software, version 26 (SPSS, Armonk, NY: IBM Corp).

RESULTS

Study population

An overall of 9,769 FMF patients and a similar number of matched controls were included (Table 1). The mean age at index date was 25.7 years (SD±18 years) and the male proportion was 49.0% for both groups. The FMF cohort had higher proportion of patients born in the Middle East (2.2% vs 1.1%; $p<0.001$), North Africa (6.9% vs 2.7%; $p<0.001$), and Turkey (0.3% vs 0.1%; $p=0.05$) compared to controls. Both groups were similar in relation to baseline comorbidities except for smoking which was slightly

higher among FMF patients (10.0% vs 9.1%; p=0.032). Thyroid and autoimmune conditions such as SLE and RA were more prevalent among the FMF group in comparison with the controls. As anticipated, chronic renal failure (3.8% vs 2.0%; p<0.001), and amyloidosis (0.7% vs 0.3%; p<0.001) were more common among FMF patients compared to controls. Of the FMF patient group, 7,630 (78.1%) received colchicine treatment for a median duration of 10.2 years (IQR 3.7-17.6 years).

Risk of osteoporosis in FMF patients

Median follow-up was 12.5 years for the FMF cohort and 12.6 years for controls. During the follow-up period, a total of 304 FMF patients were diagnosed with osteoporosis compared to 191 controls, yielding an osteoporosis incidence rate (per 10,000 persons-years) of 28.8 (95%CI 25.7-32.5) and 17.8 (95%CI 15.4-20.6), respectively, and a crude HR of 1.62 (95%CI 1.35-1.93; p<0.001) (Table 2). The association remained significant even after age and sex adjustments (HR=1.80; 95%CI 1.50-2.15; p<0.001), and robust for adjustment for all chronic comorbidities (HR=1.73; 95%CI 1.43-2.10; p<0.001). In the FMF cohort, patients were diagnosed with osteoporosis at a considerably younger age than controls (60.1 ± 12.4 vs 62.5 ±11.0 years; p=0.028).

Risk of femoral neck fracture in FMF patients

Median follow-up time was 12.5 years for both FMF patients and controls. During the follow-up period, 56 FMF patients were diagnosed with femoral neck fracture compared to 35 controls, yielding a fracture incidence rate (per 10,000 persons-years) of 5.3 (95%CI 4.0-6.9) and 3.3 (95%CI 2.3-4.6), respectively, and a crude HR of 1.60 (95%CI 1.05-2.44; p<0.05) (Table 2). The association persisted also after age and sex adjustments (HR=1.61; 95%CI 1.06-2.46; P<0.05), as well as after adjusting for all

chronic comorbidities (HR=1.58; 95%CI 1.02-2.44; P<0.001). Regarding age of diagnosis of femoral neck fractures, there was no difference between FMF patients and controls (69.8 ±13.1 vs 65.1 ±19.9 years; p=0.208). Kaplan-Meyer survival curves illustrating cumulative femoral neck fracture-free survival time between FMF and controls are included in Figure 1.

Predictors of osteoporosis or femoral neck fracture within FMF patients

In a binary logistic regression analysis, increased age (10-years-increment; OR=2.41; 95%CI 2.24-2.59; p<0.001), Arab ethnicity (OR=2.10; 95%CI 1.03-4.28; p=0.041), and North African origin (OR=1.54; 95%CI 1.16-2.04; p=0.003), were associated with higher rates of osteoporosis or femoral neck fracture (Table 3). On the other hand, male gender (OR=0.18; 95%CI 0.13-0.2; p<0.001) as well as obesity (OR=0.30; 95%CI 0.16-0.57; p<0.001) were shown to be protective factors. Chronic renal failure, a complication of FMF correlates to higher incidence of osteoporosis or femoral neck fracture (OR=1.61, 95%CI 1.12-2.32; p=0.01) whereas concomitant amyloidosis as well as autoimmune conditions such as SLE and RA did not exhibit statistically significant associations. Finally, our results found a trend towards colchicine treatment as a protective factor against osteoporosis or femoral neck fracture without reaching statistical significance (OR=0.8; 95%CI 0.56-1.15; p=0.230).

DISCUSSION

In this large population-based study, FMF was associated with increased incidence and a younger onset of osteoporosis as well as an increased incidence of femoral neck fractures. These findings remained significant even after adjustment for various confounders. Upon examining predictors of osteoporosis or femoral neck fractures

among FMF patients, older age, Arab ethnicity, North African origin in addition to chronic renal failure were positively associated with osteoporosis or femoral neck fracture incidence. In contrast, obesity was considered a protective factor, whereas colchicine treatment did not influence both examined outcomes.

While our study unveiled an increased incidence of femur fractures in the FMF group compared to controls, intriguingly, the average age of fracture occurrence remained consistent between the groups. This stands in contrast to the osteoporosis diagnosis, where a marked difference in age diagnosis was observed. One plausible interpretation for this pattern is the timely initiation of treatment following an early FMF diagnosis, potentially delaying fractures without altogether preventing them. Also, it's essential to consider that the overall fracture incidence in our cohort was relatively low, and this limited the statistical power to elucidate age differences in fracture occurrence between the two groups.

Previous studies have extensively investigated the association between osteoporosis or osteoporotic fractures and rheumatic diseases, such as SLE, RA and ankylosing spondylitis (7,8,22,23), which resulted in preventive measures recommendation including vitamin D supplementation or treatment with bisphosphonate or Denosumab (24,25). For example, a large retrospective cohort study found that RA patients had a 1.5 times higher incidence of osteoporotic fractures at typical sites, with the highest incidence for hip fractures (26).

Nonetheless, the literature regarding the relationship between FMF and osteoporosis is limited. To date, only a few cross-sectional studies have been published, evaluating small cohorts and demonstrating inconclusive results. Yildirim et al. conducted a study comparing 28 FMF patients treated with colchicine to 30 healthy controls showing

significant difference in bone mineral density (BMD) of lumbar spine, femoral neck and total femur (13). Also, in a cross-sectional study comprising 31 FMF patients, the authors showed that BMD was significantly lower compared to the control group, regardless of colchicine therapy (27). In contrast, Bindoli et al. (14) examined the BMD of forty patients with autoinflammatory conditions including FMF, Mevalonate kinase deficiency and TNF-Receptor Associated Periodic Syndrome, who were currently or previously treated with colchicine, by performing a femur and lumbar dual energy X-ray absorptiometry (DEXA) scans. No statistically significant difference between the BMD of patients compared to healthy subjects was noted. Both studies employed a case-control design and featured relatively small sample sizes, which hindered the ability to reach definitive conclusions. On the contrary, our study – a longitudinal, matched-cohort study that included 9,769 FMF patients with a mean follow-up period of 12.5 years – revealed a higher risk of developing osteoporosis and subsequently femoral neck fractures. Furthermore, the emergence of osteoporosis at a comparatively earlier age among the FMF patients accentuates the clinical significance of this association.

The mechanism explaining the increased risk of osteoporosis in patients with chronic rheumatic disease is thought to be mainly driven by inflammation, yet the exact mechanisms remain to be elucidated. Rheumatic patients are at increased risk of developing osteoporosis mainly related to the use of steroids, increased physical disability and hence, immobility and nutritional deficits (14). In contrast to autoimmune disorders, autoinflammatory disorders as represented by FMF, are not generally treated with steroids (28), eliminating one of the major secondary factors resulting in osteoporosis development. Hence, it is imperative to identify additional factors and potential causes of osteoporosis in FMF.

There is increasing evidence that inflammatory states characterized by the release of pro-inflammatory cytokines may profoundly impact the osteoclastogenesis process, giving rise to the term "osteoimmunology" (29), an emerging field trying to map the subtle interplay between the pathways of the immune system and bone. The relationship between inflammation and osteoporosis is demonstrated with the unique location of the osteoclast precursor in the bone marrow as a member of the macrophage/monocyte family (30). Accordingly, releasing of M-CSF (macrophage colony stimulating factor), essential protein for proliferation and survival of macrophages, alongside with RANKL, may lead to differentiation of precursor cell into osteoclasts (31). Illustrations of this phenomenon are demonstrated with the contribution of TNF-α (tumor necrosis factor) to the production of M-CSF, RANKL and IL (interleukin)-1 by stromal cells which consequently promoting osteoclast differentiation and activation (32). In addition, IL-1 and TNF-α prevent osteoclasts apoptosis and extend their lifespan. Moreover, IL-16 and IL-17, other pro-inflammatory cytokines, have been shown to stimulate the release of RANKL by osteoblasts and fibroblasts while also suppressing osteoblast function (9).

The inflammatory state in FMF is characterized by elevated levels of various cytokines, such as IL-1β, IL-6, IL-17 and TNF-α (33,34). Furthermore, even in attack-free periods, sub-clinical inflammation has been observed in individuals with FMF (35). The results of our study have revealed only a trend towards colchicine treatment serving as a protective factor against osteoporosis or femoral neck fracture, with no significant statistically association (OR=0.8, 95%CI 0.56 to 1.15; p=0.23). This finding implies the persistence of sub-clinical inflammatory state in these patients, even during periods of remission (36), and is independent of the therapy administered. Our conclusion is congruent with previous studies that have identified a higher prevalence of osteoporosis

among cohorts comprising adult FMF patients receiving colchicine treatment (13,15,27). Nevertheless, it is plausible that colchicine usage may be indicative of more severe manifestations of the disease in comparison to individuals who do not receive colchicine. As such, caution must be exercised when interpreting the results of comparative studies between these two groups. Taken together, it is reasonable to assume that the relationship between FMF and osteoporosis is associated to the prevalence of hyper-inflammatory states in both conditions.

Our findings demonstrated that among FMF patients, female gender and chronic renal failure are positively associated with osteoporosis and femoral neck fractures, whereas obesity is inversely related. These results align well with the literature, which has established a relationship between estrogen deficiency in postmenopausal women and increased susceptibility to osteoporosis (37). Moreover, chronic renal failure is known to induce secondary hyperparathyroidism and vitamin D deficiency, leading to reduced bone turnover and ultimately contributing to the development of osteoporosis and femoral neck fractures (38). In contrast, obesity is known to increase the BMD due to its mechanical influence on the bone architecture (39).

The current study is subject to several limitations that are inherent to its design. Firstly, the follow-up period commences with the formal diagnosis of FMF in the medical charts, however, it is acknowledged that this condition is hereditary, and it may be beneficial to consider initiating the follow-up period at birth. Secondly, the identification of patients with osteoporosis was made via a diagnostic code in the medical charts, and unfortunately, access to DEXA scans was not available, thus, it was not possible to analyze and compare the exact BMD between the groups. Furthermore, patients with FMF may exhibit a greater prevalence of concurrent medical conditions and specifically arthralgia, which plausibly constitutes a contributing factor to the

higher frequency of DEXA testing, and eventually could potentially lead to a bias in the diagnosis of osteoporosis in this group. Additionally, the study was limited by a lack of exposure to the clinical characteristics of FMF patients, such as symptoms, signs, frequency and severity of attacks, other possible pharmaceutical therapies such as steroids, as well as the specific genetic mutations in the study cohort.

It's crucial to note a statistically significant disparity in ethnicities between the FMF and control groups. This difference may introduce bias, as numerous studies have highlighted variable osteoporosis risks across different ethnic groups (40,41). Yet, as we elaborated in the introduction, FMF predominantly affects individuals of Mediterranean descent. This inherent predisposition explains the demographic variance witnessed between FMF patients and their counterparts. To mitigate the potential impact of this discrepancy, we adjusted our analyses for ethnicity. Notwithstanding this adjustment, our results consistently indicated a significantly elevated incidence of osteoporosis and femoral neck fractures in the FMF group.

In relation to other potential pharmacological interventions, as highlighted in our introduction, FMF patients are generally not treated with steroids. In instances where steroids were prescribed, possibly before a definitive FMF diagnosis, the duration of this therapy was likely brief. Consequently, such short-term usage might not significantly influence the onset of osteoporosis (42). Regarding novel therapies such as IL-1 inhibitors, it's essential to understand that our cohort mainly comprises patients diagnosed between 2000 and 2016. During this time, treatments like canakinumab and anakinra were not included in Israel's medical healthcare basket. Given this context, future research should further explore the potential effects of these medications on bone health in FMF patients.

With that being said, the present study has several strengths including being the first to explore such a large-scale population and utilization of a valid established data source which overcomes the scarcity of cases reporting FMF.

In conclusion, our study demonstrated a statistically significant increased risk of osteoporosis and femoral neck fractures among FMF patients regardless of colchicine therapy. Considering our study results, it may be worthwhile considering a routine monitoring of BMD levels at a certain stage in the disease, as well as the implementation of preventive measures such as physiotherapy, pharmaceutical intervention and fall prevention strategies to mitigate the risk of osteoporotic fractures.

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Tables

Table 1. Baseline characteristics of the study population.

Characteristics	FMF (n=9,769)	Controls (n=9,769)	p-value*
Demographics			
Age (years)			
Mean ±SD	25.7 ±18	25.7 ±18	0.987
Median (IQR)	22.4 (10-38)	22.4 (10-38)	0.875
Male gender, n(%)	4,788 (49.0)	4,788 (49.0)	1.000
Socioeconomic status, n(%)			
Low	4,525 (50.6)	4,560 (50.0)	0.462
Intermediate	3,120 (34.9)	3,074 (33.7)	0.104
High	1,305 (14.6)	1,484 (16.3)	0.002
Birth Region, n(%)			
Israel	8,528 (87.3)	7,696 (81.6)	<0.001
North Africa	670 (6.9)	261 (2.7)	<0.001
Middle East	213 (2.2)	111 (1.1)	<0.001
Turkey	25 (0.3)	13 (0.1)	0.050
Other	333 (3.4)	1,415 (14.5)	<0.001
Baseline comorbidities			
Alcohol abuse, n(%)	16 (0.2)	25 (0.3)	0.159
Smoking, n(%)	978 (10.0)	890 (9.1)	0.032
Obesity, n(%)	444 (4.5)	408 (4.2)	0.207
Diabetes, n(%)	212 (2.2)	236 (2.4)	0.251
Thyroid disorders, n(%)	186 (1.9)	144 (1.5)	0.020
Parathyroid disorders, n(%)	7 (0.1)	3 (0.0)	0.206
Lupus, n(%)	16 (0.2)	5 (0.1)	0.016
Rheumatoid Arthritis, n(%)	63 (0.6)	12 (0.1)	<0.001
Sarcoidosis, n(%)	1 (0.0)	3 (0.0)	0.317
Complications			
Amyloidosis, n(%)	73 (0.7)	33 (0.3)	<0.001
Chronic renal failure, n(%)	376 (3.8)	200 (2.0)	<0.001
Colchicine			
Ever treated, n(%)	7,630 (78.1)	--	
Duration of treatment, years			
Median (IQR)	10.2 (3.7-17.6)	--	
Mean ± SD	10.3 ± 7.0	--	

Abbreviations: FMF, familial-Mediterranean-fever.

* Student T-test, Pearson's Chi-square test.

Table 2. Incidence of osteoporosis and femoral neck fracture in FMF patients compared to controls, time to event analysis.

Outcome	Variables	FMF	Controls
Osteoporosis	Events, n	304	191
	Age at osteoporosis, mean ±SD; median (IQR)	60.1 ± 12.4; 59.8 (52-68)*	62.5 ±11.0; 62.1 (55-69)
	Follow-up time, person-years	105,480	107,068
	Follow-up time, median (IQR)	12.5 (6.8-14.6)	12.6 (7.1-14.7)
	Incidence rate per 10,000 person-years, (95%CI)	28.8 (25.7 to 32.5)	17.8 (15.4 to 20.6)
	Unadjusted HR (95%CI)	1.62 (1.35 to 1.93) **	reference
	Age-and-sex adjusted HR (95%CI)	1.80 (1.50 to 2.15) **	reference
	Multivariate¶ HR (95%CI)	1.73 (1.43 to 2.10) **	reference
Neck of Femur Fracture	Events, n	56	35
	Age at femur fracture, mean ±SD; median (range)	69.8 ± 13.1; 71.1 (62-78)	65.1 ±19.9; 70.8 (42-80)
	Follow-up time, person-years	105,718	105,813
	Follow-up time, median (IQR)	12.5 (7.2-14.4)	12.5 (7.2-14.4)
	Incidence rate per 10,000 person-years, (95%CI)	5.3 (4.0 to 6.9)	3.3 (2.3 to 4.6)
	Unadjusted HR (95%CI)	1.60 (1.05 to 2.44) *	reference
	Age-and-sex adjusted HR (95%CI)	1.61 (1.06 to 2.46) *	reference
	Multivariate¶ HR (95%CI)	1.58 (1.02 to 2.44) *	reference

¶ Adjusted for age, sex, ethnicity, socioeconomic status, obesity, smoking, diabetes, alcohol abuse, lupus, rheumatoid arthritis, sarcoidosis, thyroid dysfunction, parathyroid dysfunction, chronic renal failure, and amyloidosis.

* p-value< 0.05. ** p-value<0.001.

Abbreviations: CI, confidence interval, HR, hazard ratio, IQR, interquartile-range; FMF, familial-Mediterranean-fever.

Table 3. Predictors for osteoporosis and or femoral neck fracture within the FMF cohort, age and sex adjusted logistic regression analysis.

Variable	Osteoporosis/ Femoral neck fracture (n=340)	No Osteoporosis/ Femoral neck fracture (n=9,429)	$OR_{age\text{-}and\text{-}sex}$	95% CI	p-value
Age, years, mean ±SD	54.7 ± 13	24.7 ± 18	2.41†	2.24 to 2.59	<0.001
Male gender, n(%)	66 (19.4)	4,722 (50.1)	0.18	0.13 to 0.24	<0.001
Low SES, n(%)	129 (37.9)	4,396 (46.6)	0.89	0.69 to 1.15	0.370
Arab ethnicity, n(%)	11 (3.2)	232 (2.5)	2.10	1.03 to 4.28	0.041
Birth region					
North Africa, n(%)	118 (34.7)	552 (5.9)	1.54	1.16 to 2.04	0.003
Middle East, n(%)	48 (14.1)	165 (1.7)	1.39	0.93 to 2.08	0.107
Turkey, n(%)	3 (0.9)	22 (0.2)	0.53	0.14 to 2.05	0.355
Alcohol abuse, n(%)	1 (0.3)	15 (0.2)	1.02	0.12 to 8.40	0.981
Smoking, n(%)	41 (12.1)	937 (9.9)	0.89	0.62 to 1.28	0.539
Obesity, n(%)	12 (3.5)	432 (4.6)	0.30	0.16 to 0.57	<0.001
Diabetes, n(%)	35 (10.3)	177 (1.9)	1.09	0.71 to 1.70	0.691
Thyroid dysfunction, n(%)	22 (6.5)	164 (1.7)	0.72	0.42 to 1.22	0.221
Parathyroid dysfunction, n(%)	0	7 (0.1)	--	--	--
SLE, n(%)	2 (0.6)	14 (0.1)	2.02	0.35 to 11.70	0.432
Rheumatoid Arthritis, n(%)	10 (2.9)	53 (0.6)	1.84	0.82 to 4.11	0.139
Sarcoidosis, n(%)	0	1 (0.0)	--	--	--
Amyloidosis, n(%)	8 (2.4)	65 (0.7)	1.58	0.69 to 3.62	0.279
Chronic renal failure, n(%)	61 (17.9)	315 (3.3)	1.61	1.12 to 2.32	0.010
Colchicine (never vs ever), n(%)	45 (13.2)	2,054 (21.8)	0.80	0.56 to 1.15	0.230

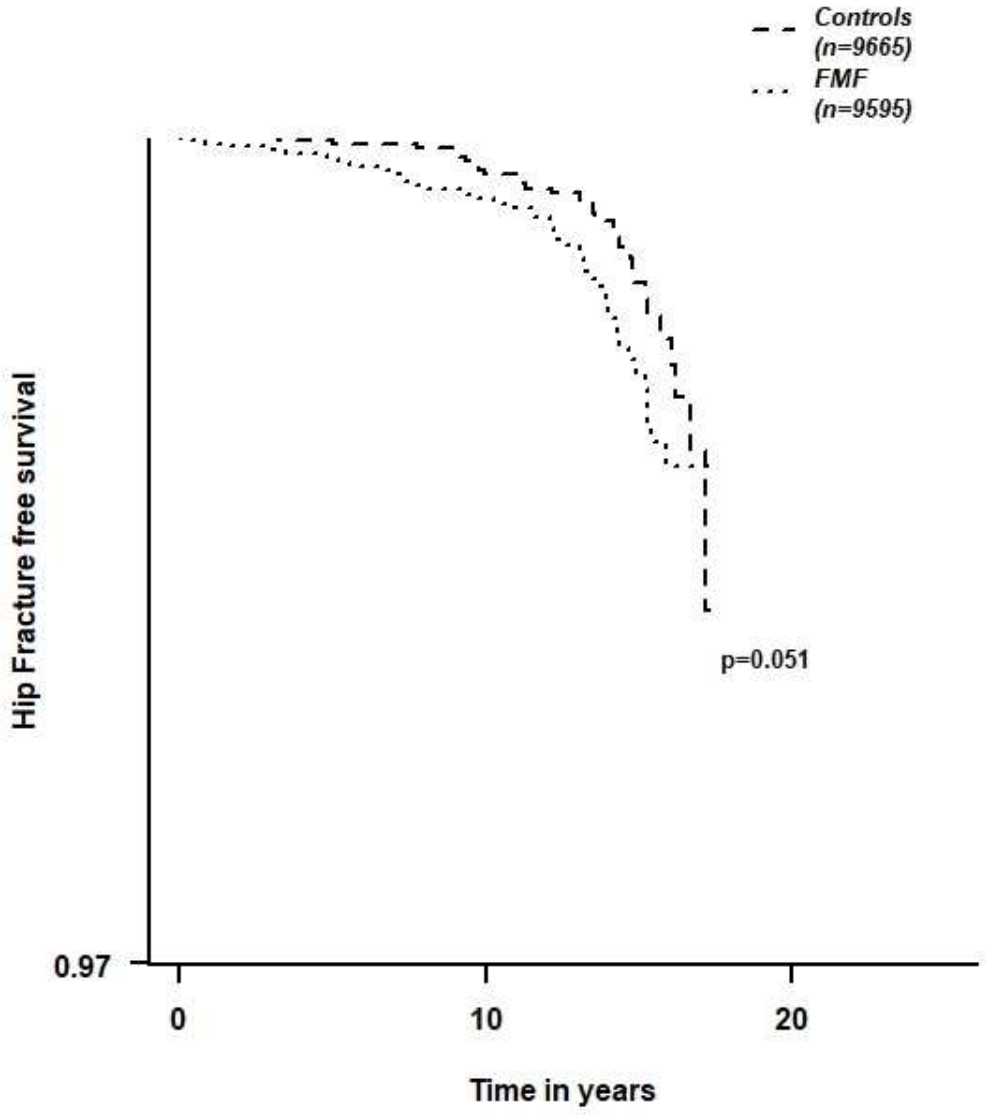
† For every 10-years increment.

¶ For every 1-year increment.

Abbreviations: CI, confidence interval; FMF, familial Mediterranean fever; OR, odds ratio; SES, socioeconomic status; SLE, systemic lupus erythematosus.

Figures

Fig. 1 Kaplan-Meyer femoral neck fractures free survival times for the FMF cohort vs. controls



Abbreviations: FMF, familial-Mediterranean-fever.

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Conflicts of interest

The authors declare they have no conflict of interest.

Informed consent

The study was exempt from obtaining informed consent due to its retrospective design.

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None.

Data availability statement:

The data used in this study is not available upon request due to the privacy policy of CHS.