BMC Rheumatology

RESEARCH

Open Access

Is middle East pain syndrome (MEPS) a variant of fibromyalgia syndrome or a distinct disease?

Mona H. Elhamamy[1], Adel A. Elbeialy[1*], Maha S. Mohamed[1], Sabah E. Abdelraheem[2] and Hala M. Elzomor[1]

Abstract

Background Fibromyalgia Syndrome (FMS) is a chronic disabling musculoskeletal condition of unknown aetiology characterized by generalized musculoskeletal pain, extreme fatigue, mood disturbance, impaired cognition, and lack of refreshing sleep. Middle East pain syndrome (MEPS) is a newly described pollution-induced syndrome of hyperparathyroidism and fibromyalgia mimicking rheumatoid arthritis, characterized by the radiological presence of spur-like excrescences in terminal phalanges. This study aimed to explore the inflammatory nature of Middle East pain and Fibromyalgia syndromes.

Methods Eighty primary fibromyalgia patients were included in this study. They were divided into two groups, group [1] 1 of 40 FMS patients with low vitamin D levels and secondary hyperparathyroidism, which were diagnosed as MEPS, and group [2] of 40 primary FMS patients. They were subjected to full medical history taking, clinical examination and laboratory assessment including serum IL-17 by enzyme-linked immunosorbent assay technique, as well as assessment of Madrid Sonographic Enthesitis Index (MASEI) using musculoskeletal ultrasound and nailfold capillaroscopic pattern assessment. Plain X-ray films for hands were done on all patients.

Results There was a statistically significant elevation of serum IL17 in the MEPS group (median = 58.3 ng/L) compared to the FMS group (median = 45.7 ng/L) as the p-value is < 0.05. Capillaroscopic examination revealed a statistically significant difference between MEPS and FMS groups regarding angiogenesis as the p-value is < 0.05. The ultrasonographic examination also showed a statistically significant difference between MEPS and FMS groups as regards MASEI score as the p-value is < 0.05. Hands X-rays evidenced the exclusive existence of tuft spur-like excrescences in MEPS patients only.

Conclusion Elevated IL-17 levels, non-scleroderma pattern capillaroscopic and enthesopathy findings in both MEPS and FMS patients are strongly supportive that inflammatory mechanisms participate in the pathogenesis of both diseases. The significant increase of these findings in MEPS than FMS patients as well as the presence of hand tufts spur-like excrescences, confirm that the newly discovered MEPS is a different disease although it involves fibromyalgia symptoms and signs.

*Correspondence:
Adel A. Elbeialy
aelbeialy@azhar.edu.eg

Full list of author information is available at the end of the article

Keywords Fibromyalgia, FMS, Middle east pain syndrome, MEPS, Interleukin17 (IL-17), Madrid sonographic enthesitis index (MASEI), Secondary hyperparathyroidism (SHPT), Parathyroid hormone (PTH)

Introduction

The symptoms of fibromyalgia (FMS), a chronic pain syndrome, include increased sensitivity to tactile stimuli, weariness, and diffuse musculoskeletal discomfort. According to the American College of Rheumatology (ACR), painful areas on the body are one of the distinguishing characteristics [1].

A recently identified syndrome resembles rheumatoid arthritis (RA) characterized by fibromyalgia, secondary hyperparathyroidism, and a chronic vitamin D3 deficit. It is an illness brought on by heavy metal contamination, including lead and cadmium. Then after, this syndrome is named Middle East Pain Syndrome (MEPS) because it was first described in the Middle East [2]. This was ascribed to many factors such as indulgence in fizzy waters, smoking, fried snacks, which all were reported to be polluted with lead and cadmium [3].

Other researchers, like Rafieian et al. [4], confirmed the existence of this disease by discovering multiple cases of bilateral hand and wrist arthritis associated with fibromyalgia and low serum vitamin D. These patients were initially misdiagnosed as having rheumatoid arthritis (RA), either seropositive or seronegative, and did not respond well to nonsteroidal anti-inflammatory drugs and disease-modifying anti-rheumatic drugs, which led to the ineffective treatment of chronic pain.

75% of MEPS patients without parathyroid gland disease have secondary hyperparathyroidism (SHPT) [2]. Despite having symptoms like RA, all MEPS patients meet both the old and new fibromyalgia syndrome criteria and do not meet any RA criteria [2]. The radiographic presence of spur-like excrescences in the finger tufts bilaterally is the primary indicator used to diagnose MEPS [2]. Chronic pain, weakness, and immunological and musculoskeletal illnesses have all been linked to hypovitaminosis D. Patients with FMS and arthritis have reported chronic pain to be related to low vitamin D levels. Nonetheless, the physiological mechanisms between pain and vitamin D remain unclear [5].

Among the central sensitization disorders, FMS works by affecting neurotransmitters and inflammatory pathways, much in the way a vitamin D deficiency works. It is well-recognized that low levels of vitamin D cause inflammatory reactions that eventually result in changes in sensitivity and chronic discomfort [6].

The aetiology and pathophysiology of fibromyalgia are intricate and multidimensional, entailing a complex interaction of immunological, neurological, and genetic components. Even though the exact mechanisms are still not fully known, recent research has shed light on the factors that contribute to the onset and maintenance of fibromyalgia. Numerous studies indicate that the pathogenesis of fibromyalgia may involve immune system dysregulation and anomalies in immunological function, such as elevated levels of inflammatory cytokines [1]. Interleukin-17, or IL-17, is a significant cytokine that plays several roles in the host's defensive mechanisms against infections of the mucosa. It is also a major pathologic cytokine in several autoimmune, inflammatory, and malignant diseases. Not only does IL-17 have roles in inflammation in vivo, but it also has a strong correlation with physiological and pathological processes [7]. Numerous autoimmune illnesses have been linked to the onset and aggravation of high levels of IL-17 [8].

The primary symptom of fibromyalgia could be caused by regional vasomotor dysregulation, which results in muscular hypoperfusion. In this regard, several investigations examining microcirculation anomalies in fibromyalgia patients have demonstrated reduced microcirculation [9].

A non-invasive diagnostic method for microvascular anomalies in a variety of rheumatologic illnesses is nailfold capillaroscopy (NFC) [10].

In people suffering from autoimmune and inflammatory rheumatic disorders, fibromyalgia is a common comorbidity. This means that these patients, especially the ones with aberrant capillaroscopic results, are also likely to develop future signs and symptoms of inflammatory rheumatic diseases and autoimmune disorders. For this subset of individuals, widespread pain may be the initial sign of an autoimmune inflammatory rheumatic disease [9].

Patients with FMS typically exhibit musculoskeletal soreness everywhere, including the entheseal sites, during a clinical evaluation. According to one study, FMS patients had a considerably higher number of sore entheses than patients with psoriatic arthritis (PsA), and it might be challenging to tell FMS patients from SpA patients who have poly-enthesitis [11].

All pathological anomalies of tendon, ligament, or joint capsule insertions, including inflammatory alterations and degenerative issues, are collectively referred to as enthesopathy [12].

Patients and methods

This study was conducted on eighty (80) patients.

(1) forty patients diagnosed with Middle East Pain Syndrome (MEPS), who have FMS, low vitamin D levels and secondary hyperparathyroidism [12]. They

were 37 females and 3 males, their ages ranged from 21 to 50 years, and they had disease duration ranging from 1 to 13 years. The cardinal sign for diagnosing MEPS is the radiological existence of spur-like excrescences in the tufts of fingers bilaterally. [Fig. 1]

(2) forty primary FMS patients with normal vitamin D and PTH levels. They were 38 females and 2 males, their ages ranged from 2 to 50 years, and they had disease duration ranging from 1 to 10 years.

Fibromyalgia was diagnosed according to the 2016 modified American College of Rheumatology Diagnostic Criteria for fibromyalgia [13] which requires the following: (1) WPI score≥7 [14] and SSS score≥5 [15], or a WPI score 4–6 and an SSS score≥9; (2) the presence of widespread pain as defined above; and (3) symptoms of at least 3 months in duration. The fibromyalgia index questionnaire (FIQ) is an assessment and evaluation instrument developed to measure fibromyalgia (FM) patient status, progress and outcomes. It has been designed to measure the components of health status that are believed to be most affected by FM. The FIQ is composed of 20 items [16].

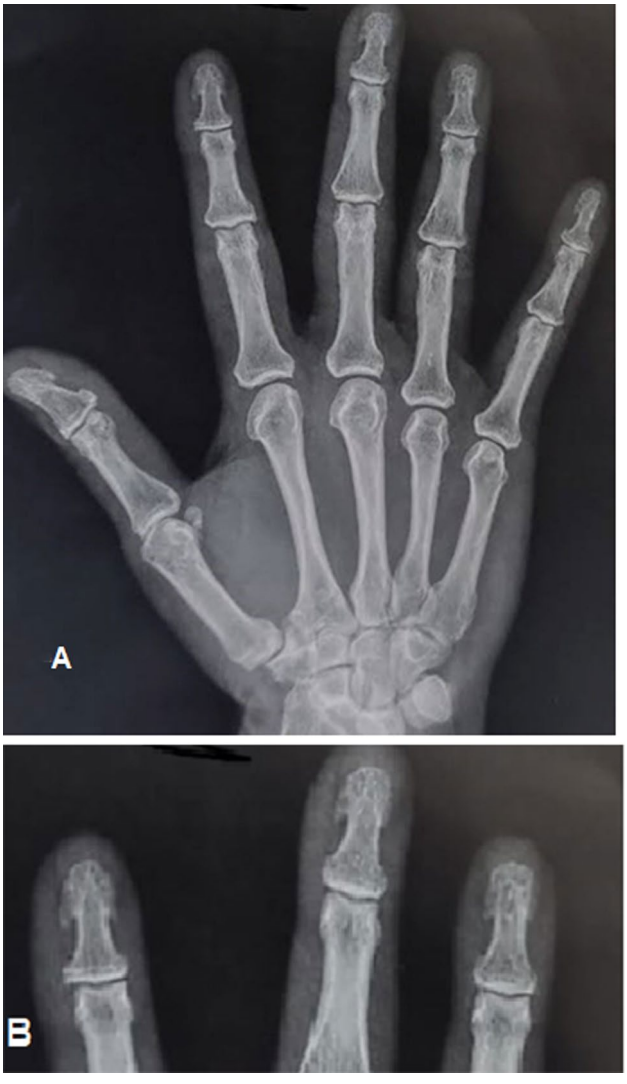

Fig. 1 Plain x-ray hand showing spur-like excrescences of terminal phalanges in MEPS patients. **A**: Right hand PA radiograph. **B**: a zoom of the distal phalanges shows the tuft spur-like excrescences

All patients were recruited from The Rheumatology and Rehabilitation department at Al-Zahraa Hospital of Al-Azhar University Faculty of Medicine for Girls from February 2023 to June 2024.

This study and its protocol have been conducted according to regulations and approval of the Ethics Committee of the Faculty of Medicine for Girls, Al-Azhar University, Nasr City, Cairo, Egypt, Registered at Central Administration of Research and Development; Egyptian Ministry of Health: Reg No. RHBIRB2018122001 (approval date, November 2022). The study was conducted according to the principles of the Declaration of Helsinki. Informed written consents were obtained from all patients for conducting the study and the publication of its results.

Exclusion criteria

Other mimicking rheumatic diseases like RA, psoriatic arthritis, erosive OA, viral arthritis, reactive arthritis, IBD arthritis, palindromic rheumatism., systemic diseases such as cardiovascular, neurologic, renal, metabolic and pregnancy or breast-feeding, patients with a history of peripheral arterial diseases or any occlusive disorder or diseases that are known to cause endothelial dysfunction (DM, chronic kidney diseases, smoking, obesity and Raynaud's phenomenon), drugs known to affect endothelial function (nitrates, lipid-lowering drugs and aspirin were stopped at least 1 week before assessment, also patients on (beta blocker, vasoactive therapies and anticoagulants) were excluded and Vasculitis.

Laboratory investigations

We conducted CBC, ESR, CRP and RF by latex agglutination, ANA by indirect IF technique, T3, T4, TSH and PTH by chemiluminescence technique on Cobas e 411 autoanalyzer and serum vitamin D3. Estimation of serum IL-17 was done by enzyme-linked immunosorbent assay (ELISA) technique. Serum IL-17 was estimated using a commercial ELISA kit from Bioassay Technology Laboratory company with Cat. No E0142Hu. The assay had a detection range of 2 ng/L – 600 ng/L and a sensitivity of 1.06 ng/L.

We did radiological Plain X-ray for hands in anteroposterior and lateral views to all patients by Toshiba Digital Radiography System DIGIX U device.

Table 1 Comparison between MEPS and FMS regarding characteristics and disease-related parameters

Studied Group Item	Middle East pain syndrome	Fibromyalgia	test	*p*-value
Sex: N. (%) - Female - Male	36 (90.0) 4 (10.0)	38 (95.0) 2 (5.0)	$X^2 = 0.72$	0.3
Age (Year) - Mean ± SD	39.5 ± 8.7	36.4 **± 9.7**	**t- test** = 1.5	0.1
Disease duration (Year) Mean ± SD	4.25 ± 3.0	3.25 ± 1.98	**t- test** = 1.7	0.08
WPI - Mean ± SD	13.6 ± 3.6	10.4 ± 3.1	**t-test** = 4.1	**< 0.001**
SSS - Mean ± SD	9.4 ± 1.3	8.4 ± 1.7	**t-test** = 1.4	0.14
FIQ - Mean ± SD	72.9 ± 11.4	68.4 ± 12.7	**t-test** = 1.6	0.09
ESR mm -Mean ± SD	22.45 ± 9.1	21.7 ± 7.9	**t-test** = 0.39	0.6
Vit D ng/ml -Mean ± SD	9.08 ± 3.3	41.7 ± 6.5	**t-test** = 24.9	**< 0.001**
PTH pg/ml -Mean ± SD	77.13 ± 31.0	31.5 ± 9.8	**t-test** = 8.8	**< 0.001**
CRP: (%)	1 (2.5%)	0 (0.0%)	$X^2 = 1.01$	0.2
RF: (%)	4 (10.0%)	1 (2.5%)	$X^2 = 1.01$	0.1
Anti-CCP: (%)	0(0.0%)	0(0.0%)	-	-

Musculoskeletal ultrasound assessment of enthesopathy and madrid sonographic enthesitis index (MASEI)

Patients were examined with commercially available equipment using a (7–11 MHz) linear phased array transducer (Xario 200, Toshiba ultrasound machine). The power Doppler (PD) frequency was set at 9.1 MHz with a pulse repetition frequency of 750 Hz. MASEI score was used in this study. It investigates six enthesis-locations bilaterally in each patient including the brachial triceps tendons, distal quadriceps, proximal and distal patellar ligaments, distal Achilles tendon, and proximal plantar fascia [17].

Nail fold capillaroscopy

The Capillaroscope device used in the study was Dinolite version 2.0 version software with a USB cable dedicated to calibrating and measuring linear dimensions and areas in magnifications: x200–600.

Statistical analysis

Recorded data were analyzed using the statistical package for social sciences, version 23.0 (SPSS Inc., Chicago, Illinois, USA). The quantitative data were presented as mean ± standard deviation and ranges when their distribution was parametric (normal) while non-normally distributed variables (non-parametric data) were presented as median with inter-quartile range (IQR). Qualitative variables were presented as numbers and percentages. Data were explored for normality using the Kolmogorov-Smirnov and Shapiro-Wilk Test. The p-value was considered significant as the following: $p \leq 0.05$ was considered significant, $p < 0.001$ was considered highly significant, and $p > 0.05$ was considered insignificant.

Table 2 Comparisons between MEPS and FMS patients as regards IL17

Studied group. Item	MEPS	FMS	*P*-value
IL-17(ng/l)	58.3	45.7	**< 0.001***
-Median	34.4	22	
-Interquartile range	515 – 29 = 486	224 – 31 = 193	
-Range			

*Tested with Mann-Whitney U

Results

Comparison between MEPS and FMS regarding characteristics, disease-related parameters scores and laboratory data

There were no statistically significant differences between MEPS and FMS groups regarding age, sex, and disease duration, ($p > 0.05$) Table (1).

It was found that there was a statistically significant difference between the two groups regarding widespread pain index [WPI] ($p < 0.05$). There were no statistically significant differences between the two groups regarding symptom severity score [SSS] and fibromyalgia impact questionnaire [FIQ] ($p > 0.05$). Table (1).

PTH was statistically significantly higher in the MEPS group (75%) than in FMS patients (0%) ($p < 0.001$), while vitamin D3 was statistically significantly lower in all MEPS patients (100%) than in the FMS group ($p < 0.05$). Table (1).

Comparison between MEPS and FMS patients as regards IL-17 level

There was a statistically significant elevation of serum IL-17 in the MEPS group (median of 58.3ng/l) compared to the FMS group (median of 45.7ng/l) $p < 0.05$. Table (2). [N.B.: (1) standard deviation was not valuable statistically here because of the wide range of levels. (2) ng/l = pg/ml]. Table (2).

Capillaroscopic findings

Capillary density

Regarding capillary density, our results showed that in the MEPS group it ranged from 7 to 12 capillary/mm with a median value of 10, while in the FMS group, it ranged from 5 to 13 capillary/mm with a median value of 11. There was no statistically significant difference between them ($p > 0.05$). [Fig. 2B]

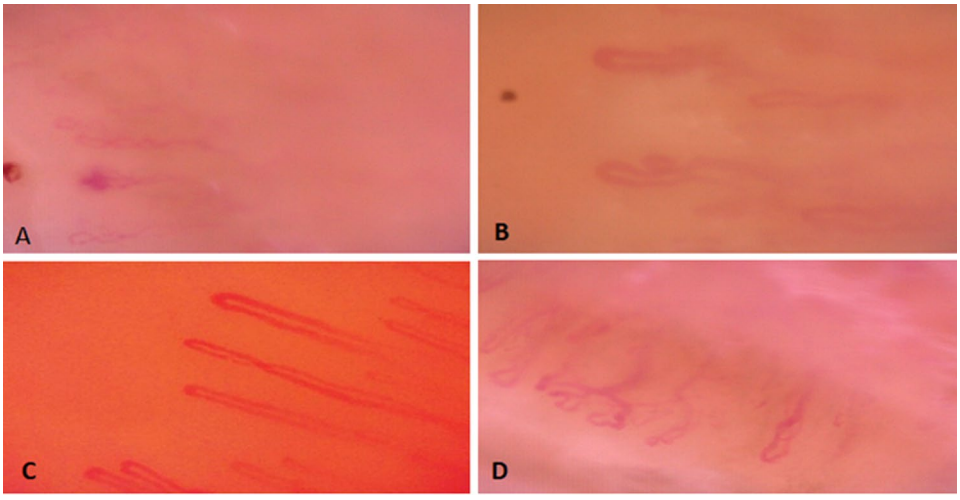

Fig. 2 Capillaroscopic findings in MEPS patients: (**A**) Microhemorrhage. (**B**) Avascular area with decreased density. (**C**) Elongated and dilated capillaries. **D**) Angiogenesis

Table 3 Comparison between MEPS and FMS groups according to capillary dimension

Studied group. Item	MEPS	FMS	test*	*P*-value
Capillary length µm	267.0	190	=519.5	**0.02**
-Median	153.25	190		
-Interquartile range	460 – 130 = 330	460 – 100 = 360		
-Range				
Capillary width µm	40.5	34.0	=568	0.7
-Median	14.5	16.0		
-Interquartile range	87 – 21 = 66	78 – 23 = 55		
-Range				

*Tested with Mann-Whitney U

Capillary dimensions

In MEPS patients, capillary length ranged from 130 µm to 460 µm with a median value of 267 µm and capillary width ranged from 21 µm to 87 µm with a median value of 40.5 µm. In the FMS group, capillary length ranged from 100 µm to 460 µm with a median value of 190 µm and capillary width ranged from 23 µm to 78 µm with a median value of 34 µm. There was a statistically significant difference between MEPS and FMS groups as regards capillary length ($p<0.05$). At the same time, there was no statistically significant difference between MEPS and FMS groups as regards capillary width ($p>0.05$). Table (3) [Fig. 2C].

Other nail fold capillaroscopic findings

Avascular area [Fig. 2B] was found in 9 (22.5%) in the MEPS group and 8 (20%) in the FMS group. Micro-Hemorrhage [Fig. 2A] was found in 4 (10%) in the MEPS group and 1 (2.5%) in the FMS group. Sub Papillary venous Plexus SPVP was found in 10 (25%) in the MEPS group and 6 (15%) in the FMS group. Angiogenesis [Fig. 2D] was found in 7 (17.5%) in the MEPS group and 0 (0%) in the FMS group. Normal U-shaped hairpin architecture was found in 16 (40%) in the MEPS group and 20 (50%) in the FMS group. Abnormally shaped capillaries were found in 12 (30%) in the MEPS group and 10 (25%) in the FMS group. Twisted capillaries were found in 10 (25%) in the MEPS group and 7 (17.5%) in the FMS group. Tortious capillaries were found in 12 (30%) in the MEPS group and 11 (27.5%) in the FMS group. Capillaroscopic parameters could not be assessed in 2 MEPS and 1 FMS patient due to dark skin. In all these parameters, there was a statistically significant difference between MEPS and FMS groups regarding angiogenesis ($p<0.05$). Table (4).

Comparison between MEPS and FMS groups regarding MASEI score

In MEPS patients, the MASEI score ranged from 0 to 40 with a median level of 26, while in FMS patients it ranged from 0 to 30 with a median level of 11.5. There was a statistically significant difference between MEPS and FMS groups as regards MASEI score ($p<0.05$). Table (5). [Figs. 3 and 4]

Table 4 Other nails fold capillaroscopic patterns

Studied group. Item	Middle East pain syndrome	Fibromyalgia	Significance test	*p*-value
Avascular area	9 (22.5%)	8 (20.0%)	$X^2=0.45$	0.7
Shape	16 (40%)	20 (50%)	X2 = 0.65	0.4
- U shape	12 (30%)	11 (27.5%)	X2 = 0.1	0.7
- Tortious	10 (25%)	7 (17.5%)	X2 = 0.7	0.3
- Twisted	12 (30%)	10 (25%)	X2 = 0.3	0.5
- Abnormal shape				
Micro haemorrhage	4 (10.0%)	1 (2.5%)	$X^2=2.3$	0.3
Pericapillary edema	10 (25%)	6 (15%)	$X^2=7.3$	0.4
SPVP	10 (25.0%)	6 (15.0)	$X^2=1.7$	0.4
Angiogenesis	7 (17.5%)	0 (0.0)	$X^2=8.2$	**0.01***

Table 5 Comparison between MEPS and FMS groups regarding MASEI score:

Studied group. Item	Middle East pain syndrome	Fibromyalgia	Test*	*p*-value
MASEI score:	40 − 0 = 40	30 − 0 = 30	= 476.0	**0.00***
- Range	26	11.5		
- Median	33.75	15		
- Interquartile range				

*Tested with Mann-Whitney U

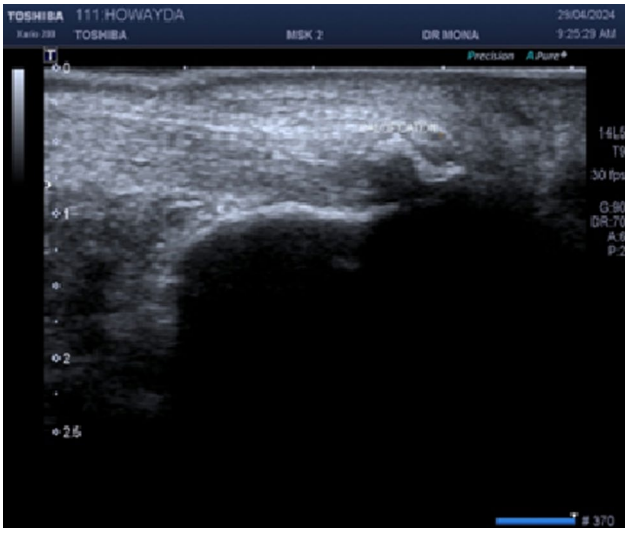

Fig. 3 Longitudinal scan showing calcification in tendo Achilles with posterior acoustic shadowing in MEPS patient

Influence of vit D3, PTH and IL17 on MASEI score in MEPS and FMS groups

In the MEPS group, there was a significant positive correlation between PTH and IL-17 with MASEI score ($p<0.001$), while there was an insignificant inverse correlation between vitamin D3 and MASEI score ($p>0.05$), while in FMS, there was only a significant positive correlation between IL-17 and MASEI score ($p<0.05$). Table (6).

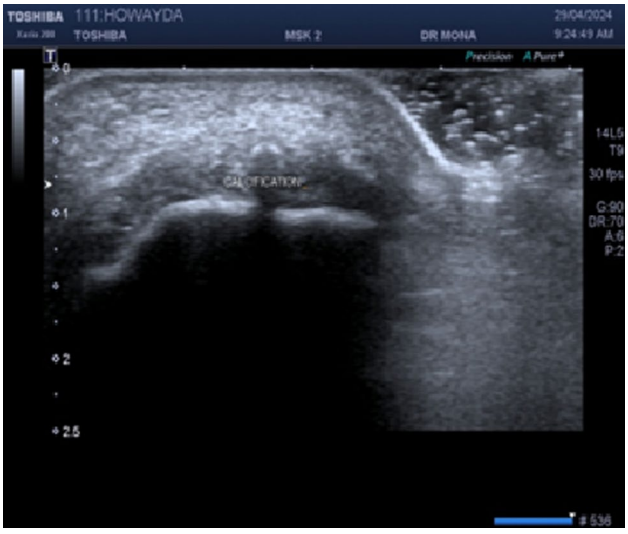

Fig. 4 Transverse scan showing calcification in tendo Achilles with posterior acoustic shadowing in MEPS patient

Table 6 Correlation between MASEI score and vit D, PTH and IL17in MEPS and FMS groups

	MASEI score	Vit D3	PHT	IL17
MEPS	r	-0.265	0.542	0.710
	P- value	0.09	**0.00***	**0.00***
FMS	r	**-0.034**	-0.281	0.657
	P- value	0.8	0.07	**0.00***

Table 7 Correlation between MASEI score and disease-related parameters in the MEPS group

Parameter	MEPS		FMS	
	r	*p*-value		
VAS	0.289	0.07	0.176	0.2
Number of tender points	-0.123	0.4	-0.115	0.4
SSS	0.525	**0.00***	0.229	0.1
FIQ	0.322	**0.04***	0.185	0.2
WPI	0.355	**0.02***	0.166	0.3

Correlation between MASEI score and disease-related parameters in MEPS and FMS groups

There were significant positive correlations between SSS, FIQ and WPI with MASEI score, in MEPS patients ($p<0.05$), while there were no statistically significant correlations between these parameters in FMS patients ($p>0.05$). Table (7).

Discussion

Middle East Pain Syndrome (MEPS) is a newly discovered disease, which may be one of the consequences of environmental pollution with heavy metals such as cadmium and lead. It was named so, because all the patients were from the Middle East [2, 4], though it might affect

people all over the world. This syndrome comprises chronic vitamin D3 deficiency or insufficiency, secondary hyperparathyroidism, and fibromyalgia (FMS).

FMS, one of the central sensitization syndromes, exerts its effects through inflammatory pathways and neurotransmitters, like the mechanism involved in vitamin D deficiency. It is known that vitamin D deficiency initiates inflammatory processes that lead to the development of chronic pain and alterations in sensitivity [6].

In this study, we aimed to investigate the inflammatory nature of MEPS and its distinction from FMS, which is one of its components. Regarding disease-related parameters, we observed a statistically significant elevation in the Widespread Pain Index (WPI) within the MEPS group compared to the FMS group ($p<0.05$).

Interleukin-17 (IL-17 A) is a key cytokine that links T-cell activation to neutrophil mobilization and activation. As such, IL-17 can mediate protective innate immunity to pathogens or contribute to the pathogenesis of inflammatory diseases, such as psoriasis and rheumatoid arthritis [(7)]. The functions of IL-17 in vivo are not only limited to inflammation but are also strongly associated with both physiological and pathological processes [7].

Previous studies tried to evaluate the elevation of IL-17 in FMS such as ***Peck et al.*** [18], who detected elevated plasma levels of IL-17 as well as tumour necrosis factor (TNF) in patients diagnosed with FMS, and ***Ellergezen et al.*** [19], who found that IL-17 is elevated in FMS and lowered with pregabalin treatment. In the current study, there was an elevation of serum IL-17 in both MEPS and FMS groups with a statistically significant elevation in the MEPS group (58.3 ng/l) compared to the FMS group (45.7 ng/l) ($p<0.05$). This means that both syndromes involve an autoimmune inflammatory process, which is exaggerated in MEPS patients.

Many studies point to FMS as an autoimmune inflammatory syndrome and the association of elevated serum levels of IL-17 with MSUS findings clarifies its potential role in developing musculoskeletal complaints [20]. ***AbdelKareem et al.*** [12], found that significant enthesopathy changes were detected among FMS patients especially affecting the Achilles, quadriceps, and proximal patellar tendons.

In our study, we found that the MASEI score ranged from 0 to 40 with a median level of 26 in MEPS patients which was statistically significantly higher than in FMS patients which ranged from 0 to 30 with a median level of 11.5 ($p<0.05$). We found the enthesis affection was in the US-B mode only, in the form of enthesophytes, loss of fibrillar pattern, thickening of tendons, bursal involvement, and bone irregularity. There was no activity in Power-Doppler US nor bony erosions. This proves that the autoimmune inflammation in MEPS is not erosive such as that found by ***Macchioni et al.*** [11], who found in Using PD- mode evaluation, ≥ 1 abnormality was noted in 59.3% of patients with PsA, 47.1% with psoriasis, and 35.3% with FMS.

Since the IL-17 A inhibitors show efficacy in treating multiple facets of SpA, including psoriasis, enthesitis, synovitis, bone erosion, new bone formation and pain, which illustrates the importance of IL-17 A in disease pathophysiology [21], we suggest that the enthesitis and high MASEI scores in MEPS our MEPS patients are due to the elevated IL-17 levels.

Nailfold capillaroscopy (NFC) is a well-established method for the assessment of structural alterations of the microcirculation. It is a crucial tool for investigating and monitoring patients presenting with Raynaud's phenomenon and vasculitis. Many studies investigated NFC in fibromyalgia patients, to see if it has a vasculitis element, such as ***Benlidayı et al.*** [9], who noted the existence of non-specific changes in capillaroscopic observations, such as more neoangiogenic capillaries, more avascular areas and more micro-aneurysms which are abnormal shape capillaries in FMS patients. ***Lambova et al.*** [22] observed the presence of capillary dilatation in 85% of the patients with primary fibromyalgia, while ***Choi and Kim*** [23] found that the capillary width was significantly decreased in FMS patients. They also found abnormally decreased digital capillary density in 67 patients with fibromyalgia.

Like this, ***Morf et al.*** [24] indicated there were significantly fewer capillaries in 10 patients with primary fibromyalgia compared to healthy controls ($P=0.001$). ***Lambova et al.*** [22], examined 26 patients with primary fibromyalgia and found no evidence of giant capillaries.

Regarding our results, we found that MEPS and FMS groups presented a non-scleroderma nonspecific pattern with minor abnormalities, like dilated, elongated capillaries and abnormal shape capillaries, some decrease in capillary density, visible SPVP, avascular area and microhemorrhage. There were no giant capillaries.

There was no statistically significant difference between MEPS and FMS groups as regards Capillary density score and capillary width ($p>0.05$), meanwhile, there was a statistically significant difference between them as regards Capillary length and angiogenesis ($p<0.05$).

Thereafter, MEPS is a more aggressive form of FMS, but the only thing which characterizes it as a new syndrome is the radiographic presence of tuft spur-like excrescences on the hand's distal phalanges bilaterally [Fig. 1]. This radiographic picture does not exist in any other disease including hyperparathyroidism, psoriatic, or rheumatoid arthritis. The only similar tuft spurs were reported in acromegaly but with a spade-like appearance [25], and a sole literature reported this sign in an unexplained case report [26].

Conclusion

Finally, we suggest that elevated IL-17 levels, enthesopathy changes, and nonspecific alterations in capillaroscopic patterns in both groups strongly support the involvement of inflammatory mechanisms in the pathogenesis of both diseases. Furthermore, the greater elevation of IL-17, the more pronounced enthesopathy, and the more significant changes in capillaroscopic patterns besides the tuft spur-like excrescences observed in the MEPS group compared to FMS suggest that MEPS may have a distinct pathogenesis from FMS. Therefore, we conclude that Middle East Pain Syndrome (MEPS) represents a newly discovered disease that warrants increased attention for accurate diagnosis, further extensive studies on its pathogenesis, and exploration of preventive and curative strategies.

Abbreviations

MEPS	Middle East Pain Syndrome a Variant of
FMS	Fibromyalgia Syndrome
IL-17	Interleukin 17
MASEI	Madrid Sonographic Enthesitis Index
ACR	American College of Rheumatology
RA	Rheumatoid arthritis
SHPT	Secondary hyperparathyroidism
NFC	Nailfold capillaroscopy
SpA	Spondyloarthropathy
PTH	Parathyroid hormone
OA	Osteoarthritis
IBD	Inflammatory bowel disease
DM	Diabetes mellitus
CBC	Complete blood picture
ESR	Erythrocyte sedimentation rate
CRP	C-reactive protein
RF	Rheumatoid factor
ANA	Antinuclear antibodies
IF	Immunofluorescence
T3, T4, TSH	Thyroid hormones
PTH	Parathyroid hormone
ELISA	Enzyme-linked immunosorbent assay
PD	Power Doppler
Hz	Hertz, MHz: Megahertz
IQR	Inter-quartile range
FIQ	Fibromyalgia impact questionnaire
SSS	Symptom severity score
WPI	Widespread pain index
SPVP	Papillary venous Plexus

Acknowledgements
Not applicable.

Author contributions
Adel A. Elbeialy (A.A.E.), Maha S. Mohamed (M.S.M), Sabah E. Abdelraheem (S.E.A.), Hala M. Elzomor (H.M.E.), Mona H. Elhamamy (M.H.E). M. H. E., A.A.E, M.S.M and H.M.E. collected study subjects' data and wrote the manuscript.M.H.E., A.A.E., MSM and H.M.E. prepared the figures. S.E.A. helped in the laboratory part of the research.All authors reviewed the manuscript.

Funding
We confirm that there are not any financial support or other benefits from commercial sources for the work reported on in the manuscript, or any other financial interests that any of the authors may have, which could create a potential conflict of interest or the appearance of a conflict of interest about the work.

Data availability
Data is provided within the related files section. for further needs contact corresponding author.

Declarations

Human ethics and consent to participate
This study and its protocol have been conducted according to regulations and approval of the Ethics Committee of the Faculty of Medicine for Girls, Al-Azhar University, Nasr City, Cairo, Egypt, Registered at Central Administration of Research and Development; Egyptian Ministry of Health: Reg No. RHBIRB2018122001 (approval date, November 2022). The study was conducted following the principles of the Declaration of Helsinki. Informed written consents were obtained from all patients to participate in this study and the publication of its results. Participants were informed of their rights, including the right to withdraw from the study at any time without any consequences. The confidentiality of all participants' data will be strictly maintained. For any inquiries, participants can contact the Ethics Committee at [aelbeialy@azhar.edu.eg].

Consent for publication
Informed written consents were obtained from all patients for the publication of its results.

Competing interests
The authors declare no competing interests.

Author details
[1]Rheumatology Department, Al-Azhar University Faculty of Medicine for Girls, 74 Ali Amin St, Nasr City, PO 11727, Cairo, Egypt
[2]Clinical Pathology Department, Al-Azhar University Faculty of Medicine for Girls, Cairo, Egypt

Received: 23 July 2024 / Accepted: 10 October 2024
Published online: 08 January 2025

References

1. Al Sharie S, Varga SJ, Al-Husinat LI, Sarzi-Puttini P, Araydah M, Bal'awi BR, Varrassi G. Unraveling the Complex web of Fibromyalgia: a narrative review. Medicina. 2024;60:272.
2. Elbeialy A, et al. A syndrome of vitamin D3 Deficiency/ Fibromyalgia/ Hyperparathyroidism Mimicking Rheumatoid Arthritis, a clinical prospective study. Open J Rheumatol Autoimmune Dis. 2021;11(2):79–88.
3. Elbeialy A, et al. Cadmium toxicity and its human health impact: a possible cause of osteomalacia and osteoporosis in polluted areas. Rheumatology. Vol. 43. Oxford: Oxford University Press; 2004.
4. Rafieian M, Mardanparvar H, Rabiei Y, Nasri H. Middle East pain syndrome as a mixture of various chronic diseases. J Parathyr Dis. 2022;10(1).
5. Martins YA, Cardinali CA, Ravanelli MI, Brunaldi K. Is hypovitaminosis D associated with fibromyalgia? A systematic review. Nutr Rev. 2020;78:115–33.
6. Ersoy S, Kesiktas FN, Sirin B, Bugdayci D, Paker N. The effect of vitamin D treatment on quality of life in patients with fibromyalgia. Ir J Med Sci (1971-). 2024;193:1111–6.
7. Mills KHG. IL-17, and IL-17-producing cells in protection versus pathology. Nat Rev Immunol. 2023;23:38–54.
8. Huangfu L, Li R, Huang Y, Wang S. The IL-17 family in diseases: from bench to bedside. Signal Transduct Target Therapy. 2023;8:402.
9. Benlidayı İC, Erdoğan EK, Sarıyıldız A. The evaluation of nailfold capillaroscopy pattern in patients with fibromyalgia. Archives Rheumatol. 2021;36:341.
10. Mansueto N, Rotondo C, Corrado A, Cantatore FP. Nailfold capillaroscopy: a comprehensive review on common findings and clinical usefulness in non-rheumatic disease. J Med Invest. 2021;68:6–14.
11. Macchioni P, Salvarani C, Possemato N, Gutierrez M, Grassi W, Gasparini S, Marchesoni A. Ultrasonographic and clinical assessment of peripheral enthesitis in patients with psoriatic arthritis, psoriasis, and fibromyalgia syndrome: the ULISSE study. J Rhuematol. 2019;46:904–11.
12. AbdelKareem MIM, Ibrahim AM, Abdelkareem MM. Musculoskeletal Ultrasound Assessment of Enthesopathy in Fibromyalgia patients. Egypt J Hosp Med. 2020;80:1027–34.

13. Wolfe F, Daniel J, Clauw M-A, Fitzcharles DL, Goldenberg W, Hauser RL, Katz, et al. 2016 revisions to the 2010/2011 fibromyalgia diagnostic criteria. Semin Arthritis Rheum. 2016;46:319–29.
14. Wolfe F, Egloff N, Winfried Häuser. Widespread pain and low widespread pain index scores among fibromyalgia-positive cases assessed with the 2010/2011 fibromyalgia criteria. J Rhuematol. 2016;43(9):1743–8.
15. Gierk B, et al. The somatic symptom scale–8 (SSS-8): a brief measure of somatic symptom burden. JAMA Intern Med. 2014;174(3):399–407.
16. Bennett R. The Fibromyalgia Impact Questionnaire (FIQ): a review of its development, current version, operating characteristics and uses. Clinical and experimental rheumatology 23.5 (2005): S154.
17. Ahmed Emerah S, Mostafa L, Kotb Y, Amer BI, Shaymaa A. Sarhan. The burden of entheseal involvement in systemic lupus erythematosus: a comparative ultrasonographic study. Clin Rheumatol. 2024;43:219–26.
18. Peck MM, Maram R, Mohamed A, Crespo DO, Kaur G, Ashraf I, Malik BH. The influence of pro-inflammatory cytokines and genetic variants in the development of fibromyalgia: a traditional review. Cureus, *12*(9), (2020).
19. Ellergezen P, Alp A, Çavun S, Çelebi M, Macunluoğlu AC. Pregabalin inhibits proinflammatory cytokine release in patients with fibromyalgia syndrome. Archives Rheumatol. 2023;38:307.
20. Ehsan K, Elsayed HM, El-Saadany NN, Elfar, Radwa M, El-Khouly SH, Almaidany RA, Gaber. Association of interleukin-17 with peripheral spondyloarthropathic changes detected by musculoskeletal ultrasound in psoriatic patients, the Egyptian rheumatologist, 42, Issue 4, 2020: 303–7, ISSN 1110–1164.
21. McGonagle DG, McInnes IB, Kirkham BW, Sherlock J, Moots R. The role of IL-17A in axial spondylarthritis and psoriatic arthritis: recent advances and controversies. Ann Rheum Dis. 2019;78(9):1167–78. https://doi.org/10.1136/annrheumdis-2019-215356.
22. Lambova SN, Muller-Ladner U. Nailfold Capillaroscopy in Rheumatology. Curr Rheumatol Reviews. 2018;14:2–4.
23. Choi DH, Kim HS. Quantitative analysis of nailfold capillary morphology in patients with fibromyalgia. Korean J Intern Med. 2015;30:531.
24. Morf S, Amann-Vesti B, Forster A, Franzeck UK, Koppensteiner R, Uebelhart D, Sprott H. Microcirculation abnormalities in patients with fibromyalgia–measured by capillary microscopy and laser fluxmetry. Arthritis Res Ther. 2004;7:1–8.
25. Killinger Z, Payer J, Lazúrová I, et al. Arthropathy in acromegaly. Rheum Dis Clin North Am. 2010;36:713–20.
26. Freyschmidt J, Brossmann J, Sternberg A et al. Freyschmidt's Koehler/Zimmer's Borderlands of Normal and Early Pathological Findings in Skeletal Radiography. 2003.

Publisher's note