Blunted sudomotor reactivity in fibromyalgia is associated with levels of depression

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Abstract

Objective

Assessment of sudomotor function by distal electrochemical skin conductance (ESC) can provide an index of peripheral neuropathy. This study explored ESC in fibromyalgia (FM) patients, controlling for tricyclic antidepressant use and Body Mass Index, and its association with the clinical severity of the disease.

Methods

ESC, clinical symptoms and an index of central pain sensitisation derived from pressure algometry were explored in thirty-three fibromyalgia patients and 33 healthy women.

Results

ESC was significantly lower in fibromyalgia patients than healthy participants. About 51% of patients exhibited moderate-to-severe ESC dysfunction, indicative of possible neuropathy. However, ESC was not related to any indicators of clinical severity, nor to algometry. ESC only correlated with depression levels; the group differences in ESC disappeared after controlling for depression. Finally, ESC was asymmetric in the overall sample, with lower values seen in the right hand relative to the left one.

Conclusion

The greater prevalence of sudomotor dysfunction in fibromyalgia patients is consistent with the presence of neuropathy in subgroups of patients, and with the basic heterogeneity of the disorder. However, neuropathy does not appear helpful for determining the clinical features of the disorders, or the level of central sensitisation measured by pressure algometry. Future studies including patients with fibromyalgia suffering and not suffering from depression as well as patients with depression but free from chronic pain, are required to identify the role of depression in the observed low ESC levels.

Key words

fibromyalgia, small fibre neuropathy, electrochemical skin conductance, central pain sensitisation, skin conductance responses

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Introduction

Abnormal epidermal nerve fibre density (ENFD) and reduced fibre diameter in patients with fibromyalgia (FM) have been observed in several studies (1-3), pointing to the presence of small fibre neuropathy (SFN) in the disease. One of the clinical presentations of SFN is the non-length dependent ganglionopathy related to impairments in C-fibres (4), which shows symptoms similar to those of FM, including cutaneous hyperesthesia, allodynia, paraesthesia, fatigue, abnormal pain sensations, etc. (5). Furthermore, FMS patients often complain of tingling, numbness, burning pain, and pain attacks (6), which are typical symptoms of neuropathic pain.

C-fibres also innervate eccrine sweat glands. Autonomic C-fibres from the sympathetic ganglia interlace the periglandular tissue with cholinergic terminals and control sweat levels (7). Sudomotor function is commonly altered in SFN, and seems to be reduced in FM patients (8-11). One validated method for assessing sudomotor function is through electrochemical skin conductance (ESC), a simple electrophysiological test that evaluates the density of sweat glands containing functional chloride channels that has been proposed as a possible indirect marker of SFN (12). To date, only two studies have explored sudomotor function through ESC assessment in FM patients. The first one, by Pickering et al. (8), observed a significant sudomotor dysfunction and its lateralisation in the dominant hand of FM patients in comparison to healthy individuals. The second study, by Dumolard *et al.* (11), examined ESC in a large cohort of FM patients and reported that 20% of the total patient sample has reduced ESC values, which were weakly related to greater central sensitisation symptoms and depression. Likewise, the lower tonic skin conductance (SC) observed in FM patients (9, 10), and the blunted SC responses in this population (9) suggest alterations of sweating function in FM. Furthermore, a weak but significant inverse association was observed between SC parameters and current pain intensity and fatigue (9), and tonic SC was inversely associated with an index of central pain sensitisation in FM patients (slow repeated evoked pain; see also below) (10). These results suggest that peripheral neuropathy could promote the development of central pain sensitisation.

The present study aims to (1) corroborate the previous observed differences between FM patients and healthy individuals in sudomotor function by analysing ESC responses. Two relevant variables not controlled for in the previous studies are the use of antidepressants and body mass index (BMI). The use of antidepressants is common in FM patients and these drugs, especially tricyclics like amitriptyline, have an anticholinergic effect that reduce sweating (10, 13). Higher BMI and obesity prevalence are commonly observed in FM patient samples (14). Obesity may promote the development of peripheral neuropathy in distal locations like the feet (15). Thus, previous findings of reduced sudomotor function in FM might be confounded by the large use of antidepressants and the higher prevalence of obesity in this population. These two variables were controlled for in the present study. Furthermore, the study also aims to (2) explore associations of sudomotor function with the chronicity and severity of clinical symptoms of FM (*i.e.* depression, anxiety, fatigue, neuropathic pain, etc.), as well as central sensitisation to pain measured by a dynamic evoked pain protocol; (3) determine possible differences in the clinical profiles of FM patients with and without alterations in ESC levels; and (4) explore the lateralisation of sudomotor function, as assessed by ESC.

Methods

Participants

Considering the greater prevalence of FM in women (which is similar to the ratio present in other chronic pain diseases) (16), and in order to avoid possible confounding related to sex, this study only recruited females; 33 women with FM and 33 healthy women (control group) participated. All participants were right-handed. The FM patients were recruited through the Fibromyalgia Association of Jaén (Spain) and all

of them met the 2010 American College of Rheumatology criteria (17) for FM according to medical records provided by rheumatologists. Exclusion criteria comprised the presence of metabolic, inflammatory, cardiovascular, or neurological disorders, as well as severe somatic (*e.g.* cancer) or psychiatric (*e.g.* psychotic or drug abuse) conditions.

Two additional exclusion criteria were the use of tricyclic antidepressants and suffering class II obesity due to its possible confounding effects on the results (10, 14, 15). To justify these additional criteria, we conducted two pilot studies. In one study we measured ESC in five FM patients taking tricyclic antidepressants, observing lower values relative to the current patients with FM (59.02±10.91 *vs.* 77.53±7.06 μS [mean of the four body locations, see later]; $t(36) = -5.08$, $p<.0001$). In the other pilot study we evaluated three patients with class II obesity (BMI ≥35), also finding lower ESC values in these patients relative to the current patient sample (65.54±6.24 *vs.* 77.53±7.06 μS [mean of the four body locations]; $t(34) = -2.83$, $p=0.008$). FM chronicity (age at assessment minus age at which FM symptoms first appeared) was 21.05±12.00 years. The control group was composed by women free from chronic pain conditions, similar to the patients in terms of sociodemographic variables and recruited with the same exclusion criteria used for FM patients.

Sudomotor assessment

ESC was recorded using the SUDOSCAN® device (Impeto, Paris, France). This device measures the capacity of the sweat glands to release chloride ions in response to electrical stimulation. It evaluates sudomotor function in the palms of the hands and soles of the feet, in which the density of sweat glands is higher. A low DC voltage (≤4 volts) is applied to the hands or feet to generate a current relative to the flux of chloride (ion) supplied by the sweat glands. ESC is calculated for each hand and foot based on the current generated and voltage supplied. As well as measuring the ESC, the SUDOSCAN® classifies patients into one of three categories according to the ESC value: no dysfunction (60/70 to 100μS), moderate dysfunction (40/50 to 60/70μS) or severe dysfunction (0 to 40/50 μS). A high ESC has been associated with normal sweat function and small C-fibre innervation; lower ESC suggests peripheral or autonomic neuropathy (12).

Evoked pain assessment

Pain threshold and tolerance were measured by a mechanical pressure algometer (JTECH Medical, Midvale, UT, USA) connected to a computer. The computer provided feedback regarding the actual pressure exerted, which must be increased at 1kg/s. The algometer was inserted into a piston, which allows for the exertion of a constant and precise pressure on the fingernail (over a $1cm^2$ surface). To assess the experience of pain, a 10-cm visual analogue scale (VAS) was used. The anchor points of the scale were "no pain" and "extremely painful". The pain threshold was defined as the pressure at which the participant started to feel pain and tolerance as the maximum pressure tolerated.

The slowly repeated evoked pain (SREP) protocol was applied to obtain an indicator of pain sensitisation. The protocol involved nine repeated stimulations on the fingernail of the third finger of the left hand with a pressure intensity individually calibrated to evoke moderated pain intensity in all participants [Intensity= Threshold+ (Tolerance-Threshold)/4 *1.25]. The participant rated the pain evoked by each stimulus using the VAS described above. The SREP sensitisation index is the difference in pain intensity (VAS ratings) between the last (9^{th}) and first pain stimulus. A larger positive value denotes greater pain sensitisation. More details of the procedure are provided by de la Coba *et al.* (18, 19).

Clinical assessment

Clinical pain was assessed using the Spanish versions of the McGill Pain Questionnaire (MPQ) (20) and the Neuropathic Pain Symptom Inventory (NPSI) (21). The MPQ assesses quantitative and qualitative aspects of pain, such as location, quality, temporal properties, and intensity. In this study, the total score was obtained for the analysis. A Cronbach's α value of 0.75 was reported for the Spanish version of the MPQ (20). The NPSI is a 12-item self-report instrument that assesses the different qualities and types of neuropathic pain symptoms. Items are scored on a numerical scale (range: 0–10). A score ≥50 indicates possible neuropathic pain (22). The Cronbach's α (internal consistency) of the total score for the Spanish version of the NPSI is 0.70 (21).

Central sensitisation symptoms were examined using the Spanish version of the Central Sensitisation Inventory (CSI) (23). A score ≥40 is the cut off for possible central sensitisation and a score ≥60 indicates extreme central sensitisation symptoms (24). The Spanish version has high internal consistency (Cronbach's $\alpha = 0.87$) (23).

The possible effect of pain catastrophising on the SREP response was controlled for by using the Catastrophising subscale (a 6-point Likert scale) of the Spanish version of the Coping Strategies Questionnaire (25) (Cronbach's α of 0.89).

Fatigue was evaluated by the Spanish version of the Fatigue Severity Scale (26), which is a 9-item scale that provides a total fatigue score (range: 0–63). The internal consistency of the Spanish version is $\alpha=0.88$.

Insomnia was assessed by the homologue subscale of the Oviedo Sleep Questionnaire (27). This subscale consists of 10 items (range: 0–50) that measure sleep quality. The internal consistency of the questionnaire is $\alpha=0.77$.

Anxiety was evaluated by the State-Trait Anxiety Inventory (Spanish version) (28). This instrument assesses current and habitual anxiety levels (20 items each) using a 4-pointLikert scale (score range: 0-60). Trait Anxiety subscale (STAI-T) was the used in the present study, which has an internal consistency of $\alpha=0.87$. A score greater ≥33 indicates a greater anxious propensity (28).

Depression levels were assessed by the Spanish adaptation of the Beck Depression Inventory (BDI) (29). This is a 21-item scale, with a score range from 0 to 63. The Cronbach's α (internal consistency) is 0.95. A score ≥20 indicates moderate-to-severe depression symptoms (30).

Procedure

The study involved one session around 90 minutes in length, and data was collected from May 2021 to June 2022. First, the clinical evaluation was completed and the questionnaires were administered; this was followed by the algometry evaluation and, finally, the sudomotor function assessment. When assessing ESC, the metal plates must be positioned correctly on the participant before starting the scan, with their bare feet on foot sensor plates and the palms contacting hand sensor plates.

The participants were telephoned in advance and asked to avoid the use of skin cream on the palms of the hands and soles of the feet in the 48 hours before the study, and to not consume coffee/tea or perform physical exercise on the day of the study. The participants were not asked to stop their usual medication to perform the study, except for analgesics. They were asked to avoid the use of analgesic medication on the day before the study, unless they considered this impossible due to pain; in such cases, the study was postponed for 1 day. Participants were informed about the study procedure and completed the informed consent form. All of them were registered in the database individually with an identification code. The Ethics Committee of the University of Jaén approved the study.

Statistical analysis

In order to determine the optimal sample size based on the expected effect sizes, the G*Power 3.1.7 programme (University of Düsseldorf, Germany) was used (31). Assuming an effect size (f) of 0.40 [based on Pickering *et al*. (8)], and an alpha level of 0.05, a sample size of >25 participants per group was estimated to be required to achieve a power of 0.80. The normality of the data was assessed using the Kolmogorov-Smirnov test (all cases $p>0.05$). General group comparisons were performed using Student's t-test for indpendent samples. Associations between variables were analysed using Pearson correlations and multiple linear regression analysis. For the analysis of the sudomotor variable and comparison of patients with *vs*. without ESC dysfunction, ANCOVA models were constructed; BMI was included as a covariate because the patients had a marginally higher BMI than the healthy participants (Table I). Moreover, considering the possible confounding effect of pain catastrophising on SREP sensitisation (18), ANCOVA including catastrophising as a covariate was conducted to analyse group differences in SREP sensitisation. Repeated-measures ANOVAs with right hand/foot *vs*. left hand/foot as a within-group factor were used to analyse the lateralisation of ESC. In all of these latter analyses, 1000 bootstrap replications were performed to obtain 95% confidence intervals.

Table I. Demographic and clinical data from patients with fibromyalgia (FM) and healthy participants.

	FM patients (n=33) Mean±SD	Healthy women (n= 33) Mean±SD	t or χ^2	p
Age	49.12 ± 9.50	51.36 ± 5.28	-1.18	0.245
BMI	26.67 ± 3.69	25.12 ± 3.73	1.83	0.072
Antidepressants*[1] (%)	7 (21.21)	3 (9.09)	1.89	0.303
Anxiolytics (%)	3 (9.09)	2 (6.06)	0.22	1.00
Analgesics (%)	15 (45.45)	2 (6.06)	13.39	<0.001
Opioids (%)	10 (30.30)	0	11.79	<0.001
Pain threshold	2.99 ± 1.26	4.41 ± 1.47	-4.20	<0.001
Pain tolerance	5.50 ± 2.18	6.90 ± 1.89	-2.79	0.007
SREP sensitisation	1.67 ± 1.48	0.18 ± 0.73	5.20	<0.001
Pain catastrophising	17.06 ± 7.90	5.36 ± 7.14	6.31	<0.001
CSI	59.27 ± 11.25	26.42 ± 12.30	11.32	<0.001
MPQ Total	53.12 ± 21.51	7.39 ± 10.48	10.98	<0.001
NPSI Total	50.88 ± 18.34	4.27 ± 7.48	13.52	<0.001
Fatigue (FSS)	49.15 ± 11.26	16.00 ± 10.09	12.60	<0.001
Insomnia (OSQ)	29.70 ± 9.06	14.67 ± 5.76	8.04	<0.001
Depression (BDI)	16.18 ± 7.64	5.85 ± 4.88	6.55	<0.001
Trait Anxiety (STAI-T)	38.36 ± 12.36	31.30 ± 9.72	2.58	0.012

BMI: body mass index; SREP: slowly repeated evoked pain; CSI: central sensitisation inventory; MPQ: McGill pain questionnaire; NPSI: neuropathic pain symptoms inventory; FSS: fatigue severe scale; OSQ: Oviedo sleep questionnaire; BDI: Beck Depression Inventory; STAI-T: State-Trait Anxiety Inventory-Trait.
*Antidepressants with no anticholinergic effects.

Results

Clinical and demographic variables

Patients reported higher levels of clinical pain (including neuropathic pain), central sensitisation, pain catastrophising, fatigue, insomnia, anxiety and depression compared to healthy participants. Furthermore, they had a lower pain threshold and less pain tolerance, as well as greater SREP sensitisation (Table I). After controlling for pain catastrophising, the group difference in SREP sensitisation remained [$F(1, 63)=13.39$, $p<0.001$, $\eta^2=0.175$]. BMI was marginally higher in the FM patients than healthy participants, and was therefore controlled for in subsequent analyses. The majority of the FM patients (96.97%) reported clinically relevant central sensitisation symptoms (32 patients with CSI ≥40 *vs*. 4 healthy women with CSI ≥40; $\chi^2=47.91$, $p<0.001$). Moreover, 42.42% of FM patients had extreme central sensitisation symptoms (14 with CSI ≥60) whereas no healthy women had such symptoms ($\chi^2=17.77$, $p<0.001$). Clinically relevant neuropathic pain was observed in 75.76% of FM patients (25 patients with NPSI ≥50), but was not seen in any healthy women ($\chi^2=40.24$, $p<0.001$). Greater levels of clinical anxiety and depression were observed in the FM patients: 75.76% exhibited a propensity toward anxiety compared to 45.45% of the healthy women (25 patients *vs*. 15 healthy women with a STAI-T ≥33; $\chi^2=6.35$, $p=0.012$). Finally, 30.30% of the FM patients had moderate-to-severe depression compared to 0% of healthy women (10 patients *vs*. 0 healthy women with a BDI score ≥20; $\chi^2=11.79$, $p<0.001$).

Group differences in sudomotor function

All recorded ESC (both hands and feet)

Table II. Means ± standard deviations of electrochemical skin conductance (ESC) in patients with fibromyalgia (FM) and healthy participants.

	FM patients (n=33) Mean ± SD	CI 95% Lower-Upper	Healthy women (n=33) Mean ± SD	CI 95% Lower-Upper	*t*	*p*
ESC (r.h)	62.66 ± 15.27	57.89–67.43	72.26 ± 10.20	68.43–75.31	-3.00	0.004
ESC (l.h)	65.77 ± 13.53	61.65–70.08	74.68 ± 10.24	70.85–77.83	-3.02	0.004
ESC (r.f)	78.82 ± 6.86	76.48–81.01	81.94 ± 5.11	80.05–83.63	-2.10	0.040
ESC (l.f)	78.23 ± 7.60	75.71–80.75	81.26 ± 6.12	79.95–83.70	-1.78	0.080

r/l. h: right/left hand; r/l. f: right/left foot. ESC was measured in μS.

Table III. Electrochemical skin conductance (ESC) range rates in the four extremities in patients with fibromyalgia (FM) and healthy women samples.

	FM patients (n=33)			Healthy women (n=33)		
	Normal ESC (%)	Moderate dysfunction (%)	Severe dysfunction (%)	Normal ESC (%)	Moderate dysfunction (%)	Severe dysfunction (%)
Right hand	19 (57.58)	12 (36.36)	2 (6.06)	29 (87.88)	4 (12.12)	0
Left hand	20 (60.61)	12 (36.36)	1 (3.03)	30 (90.91)	3 (9.09)	0
Right foot	30 (90.91)	3 (9.09)	0	33 (100)	0	0
Left foot	26 (78.79)	7 (21.21)	0	30 (90.91)	3 (9.09)	0

Table IV. Clinical severity in sub-groups of fibromyalgia patients with moderate/severe electrochemical skin conductance (ESC) dysfunction and without ESC dysfunction.

	No ESC dysfunction (n=19) Mean±SD	Moderate/severe ESC dysfunction (n=14) Mean±SD	*F* or X^2	*p*	η_2 or Cramer's V
Pain threshold	2.94 ± 1.01	3.06 ± 1.57	0.97	0.332	0.031
Pain tolerance	5.21 ± 1.62	5.90 ± 2.80	2.26	0.143	0.070
SREP sensitisation	1.65 ± 1.47	1.70 ± 1.55	0.05	0.826	0.002
CSI	58.79 ± 10.03	69.93 ± 13.11	0.02	0.962	<0.001
MPQ total	54.95 ± 25.79	50.64 ± 14.37	0.22	0.646	0.007
NPSI total	50.32 ± 20.10	51.64 ± 16.35	0.13	0.911	<0.001
Fatigue (FSS)	47.89 ± 10.14	50.86 ± 12.81	0.07	0.788	0.002
Insomnia (OSQ)	29.42 ± 9.58	30.07 ± 8.66	0.01	0.982	<0.001
Depression (BDI)	13.32 ± 5.00	20.07 ± 8.99	6.10	0.019	0.169
Trait Anxiety (STAI-T)	37.84 ± 12.31	39.07 ± 12.86	0.10	0.757	0.003
Chronicity [in years]	21.26 ± 12.04	19.14 ± 10.27	0.64	0.439	0.020
Antidepressants* (%)	4 (21.05)	3 (21.43)	<0.001	1.00	0.979
Anxiolytics (%)	1 (5.26)	2 (14.29)	0.79	0.561	0.373
Analgesics (%)	8 (42.11)	7 (50.00)	0.20	0.733	0.653
Opioids (%)	5 (26.32)	5 (35.71)	0.34	0.707	0.561

SREP: slowly repeated evoked pain; CSI: central sensitisation inventory; MPQ: McGill pain questionnaire; NPSI: neuropathic pain symptoms inventory; FSS: fatigue severe scale; OSQ: Oviedo sleep questionnaire; BDI: Beck depression inventory; STAI-T: State-Trait Anxiety Inventory-Trait.
*Antidepressants with no anticholinergic effects.

were significantly lower in FM patients than healthy participants, except for ESC in the left foot (where the difference was marginally significant) (Table II). After controlling for BMI, the ANCOVAs revealed significant group differences in ESC in the right hand [$F(1,63)=8.02$; $p=0.006$, $\eta^2=0.113$] and left hand [$F(1,63)=8.11$; $p=0.006$, $\eta^2=0.114$]. The group difference remained marginally significant for the right foot [$F(1,66)=3.20$; $p=0.079$, $\eta^2=0.048$] but did not reach significance for the left foot [$F(1,63)=2.05$; $p=0.157$, $\eta^2=0.031$].

Associations between sudomotor function and clinical symptoms in FM patients

ESC only showed a significant inverse correlation with depression levels [right hand: r= -0.40, $p=0.020$; left hand: r= -0.39, $p=.024$; right foot: r= -0.56, $p=0.001$; left foot: r= -0.61, $p<0.001$] and BMI [right foot: r= -0.37, $p=0.035$; left foot: r= -0.43, $p=0.014$; right hand (trend):r= -0.31, $p=0.077$]. The association between ESC and depression was maintained after controlling for BMI, except for the left hand [right hand: β= -0.35, t= -2.06, $p=.048$, $r^2=0.20$, 95% CI: -1.52– -0.08 (*unstandardised* β = -0.70); left hand: β= -0.33, t= -1.95, $p=0.061$, $r^2=0.20$, 95% CI: -1.33– -0.01 (*unstandardised* β = -0.59); right foot: β= -0.50, t= -3.30, $p=0.003$, $r^2=0.37$, 95% CI: -0.71– -0.14 (*unstandardised* β = -0.45); left foot: β= -0.53, t= -3.75, $p=0.001$, $r^2=0.44$, 95% CI:-0.79– -0.24 (*unstandardised* β= -0.53)]. The significant association of overall ESC (average of the four members) with depression in FM patients [β= -0.44, t= -2.82, $p=0.008$, $r^2=0.32$, 95% CI: -1.08– -0.12 (*unstandardised* β = -0.57)] is depicted in Figure 1. Comparison of ESC between FM patients without depression (n=23) and those with clinically relevant depression (BDI ≥20; n=10) showed lower ESC in the depressed patients (65.19±9.73 *vs*. 74.06±8.67 μS, respectively; t(31) = 2.60, $p=0.014$).

When depression was included as a covariate in the ANCOVA models, all prior group differences in ESC disappeared, thus confirming its relevance to ESC levels [right hand: $F(1, 63)=0.69$, $p=0.409$, $\eta^2=0.011$; left hand: $F(1, 63)=0.72$, $p=0.401$, $\eta^2=0.011$; right foot: $F(1, 63)=0.26$, $p=0.613$, $\eta^2=0.004$; left foot: $F(1, 63)=0.49$, $p=0.485$, $\eta^2=0.008$].

Clinical profiles of FM patients with and without ESC dysfunction

Among the total FM sample, 17 patients (51.51%) showed moderate-to-severe sudomotor dysfunction in at least one extremity, compared to only 5 participants in the healthy sample ($\chi^2=9.81$, $p=0.002$). Severe ESC dysfunction was only recorded in the hands (one FM patient in both hands, and one in the left hand) (Table III).

Comparisons of clinical variables between patients who showed no ESC dysfunction in their hands (n=19) and those who did show such dysfunc-

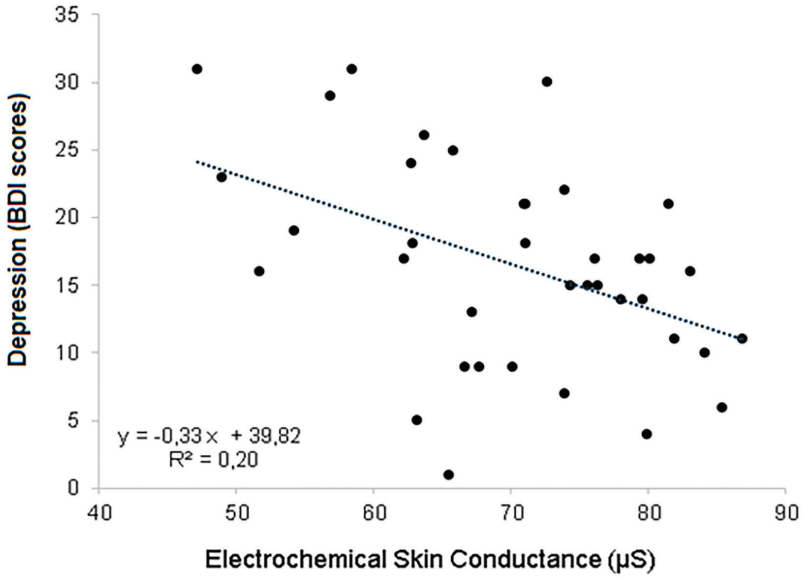

Fig 1. Scatterplot and regression line for the association between depression levels and overall average of electrochemical skin conductance in fibromyalgia patients.

tion (n=14) after controlling for BMI, are displayed in Table IV. Excepting depression, which was greater in patients with ESC dysfunction, no other significant differences arose in any of the assessed variables between the two subgroups of patients.

Lateralisation of sudomotor function

We observed ESC lateralisation; lower ESC levels were seen for the right hand [main effect of lateralisation: $F(1,64)= 39.17$, $p<0.001$, $\eta^2=0.376$] in both FM patients and healthy participants [lateralisation × group interaction: $F(1,64)= 0.60$, $p=0.440$, $\eta^2=0.009$]. Although the effect was of much lower magnitude, lateralisation was also found for the feet, but in this case lower values where observed for the left foot (main effect of lateralisation [$F(1,64)= 4.84$, $p=0.031$, $\eta^2=0.069$)] regardless of group [lateralisation × group interaction: $F(1,64)=0.03$, $p=0.871$, $\eta^2<0.001$].

Discussion

Patients with FM showed a significant reduction of sudomotor function in the hands, in comparison to healthy women, even after controlling for BMI. Given that sweating is controlled by the sympathetic branch of the autonomic nervous system, these results are congruent with the lower autonomic reactivity observed in FM patients to both mental and physical stressors (9, 32-34). It was previously found that FM patients had diminished sudomotor function only in the dominant hand in comparison to healthy women (8), while in our study this reduction was observed in both hands, and to a lower extent in the feet. In fact, severe ESC dysfunction was only found in the hands of the FM patients. A higher prevalence of ESC dysfunction was found in the FM sample relative to healthy participants, which accords with previous studies that observed a higher prevalence of small fibre pathology in this chronic pain condition (1, 35).

One strength of the present study was that we controlled for tricyclic antidepressants (like amitriptyline) and BMI. A high proportion of FM patients use this antidepressant medication (36) to manage pain. Furthermore, amitriptyline is commonly used due to its effectiveness in improving sleep, fatigue, and overall quality of life (37). Given the strong anticholinergic effects of tricyclics (10) a question arises as to whether the previously reported lower ESC values in FM were attributable to FM itself, or to the use of tricyclics. Regarding BMI, which is usually higher in FM patients than healthy individuals and seems to be associated with the severity of the symptoms (38), we found a negative association between ESC and BMI. We excluded patients with class II obesity and controlled for the effect of BMI in the analyses. Controlling both of these relevant variables facilitates interpretation of the sudomotor results obtained in our study.

Sudomotor dysfunction was observed only in a subset of patients. In our study, 51.51% of patients showed moderate-to-severe dysfunction in at least one location. These results are in line with previous studies that proposed that there is heterogeneity of the mechanisms underlying FM and the existence of pathophysiologic subgroups of this population (33, 39, 40). ESC can be a useful way to detect the loss of small nerve fibres (12) and review studies have revealed impairment of these fibres (analysed through different methods) in approximately 50% of patients with FM (41). This is similar to the percentage of patients with some degree of sudomotor dysfunction in our study. In the study of Pickering *et al*. (8), reduced ESC levels in the dominant hand were observed in a higher proportion of patients (28%) than healthy volunteers (12%), although this prevalence was lower than in our study. In a large cohort study of FM patients, also a lower incidence of reduced ESC values was reported (53/265 cases, *i.e*. 20%) (11). A possible explanation for the greater prevalence of sudomotor dysfunction in our study could be the much greater disease chronicity of our patient sample (around 21 years) than that reported in the two previous ESC studies.

As expected, our FM patients showed significantly lower pain thresholds/tolerance than the healthy controls, similar to previous studies (18, 32). More-over, pain sensitisation, as measured by the SREP protocol, was observed in FM patients but not in healthy participants, as reported previously (18). SREP is characterised by increased perceived pain intensity with repetition of the stimulus, which is in line with the notion of central sensitisation to pain in FM patients (42). In the present study, we used the SREP protocol for a more direct assessment of central sensitisation, beyond merely self-reported symptoms (obtained using the CSI). None of the

evoked pain variables (pain threshold, tolerance or SREP sensitisation) correlated with the ESC. This is in line with reports of a lack of any correlation between ESC and diffuse noxious inhibitory control or thermal pain thresholds in FM patients (8). Taken together, these results suggest that, although C-fibres are involved in both sweating and pain processing, the degree of affectation of sweat glands or autonomic C-fibre activity does not affect pain processing. This topic requires further exploration in future studies; in particular, A-delta fibres should be evaluated.

Our patients reported more severe pain catastrophising, central sensitisation, clinical pain and neuropathic pain than the control group, in accordance with previous studies (1, 43). This is also in accordance with the fact that the majority of the FM patients in this study had clinically relevant and extreme central sensitisation symptoms and neuropathic pain, similar to the results reported by Dumolard *et al*. (11).

Sudomotor function did not correlate with clinical symptoms, and was only associated with depression levels in the FM sample, which remained after controlling for BMI. This is congruent with the weak but significant (r= -0.14, p=0.022) association between ESC levels (only in the hands) and depression in a large previous cohort study of FM patients (11). This association is in line with previous findings of lower basal autonomic activity in FM patients with comorbid depression relative to FM patients without depression, as reflected in several cardiovascular variables (including some controlled by the sympathetic system, such as stroke volume and left ventricular ejection time) (33). Furthermore, studies of patients suffering major depressive disorder or dysthymia reported lower autonomic cardiovascular reactivity in general parameters related to sympathetic activity, such as systolic and diastolic blood pressure, as well as in sympathetic-specific parameters such as pre-ejection period, compared to healthy participants (44, 45). The results of our study point to a role of depression in determining ESC levels. In fact, when depression levels were statistically controlled, the previously observed group differences in ESC disappeared. These results suggest that the lower sudomotor function of the sample of FM patients may not be due to FM itself, but rather to the comorbid depression commonly observed in this population. Therefore, future studies of sudomotor function in FM should control for levels of depression. Alternatively, considering the high prevalence of depression in FM (46), patients suffering from depression but free from pain should be included as another comparison group.

The absence of differences in clinical variables between the subgroups of FM patients with and without sudomotor dysfunction was coherent with the lack of associations between ESC levels and clinical symptoms (excepting depression). This further suggests that reduced ESC (*i.e*. probable distal neuropathic affectation) does not predict the clinical severity of FM. A lack of any correlation between ESC and clinical symptoms has been reported previously (8, 12). However, Dumolard *et al*. (11) found a weak but significant association between ESC levels in the hands and symptoms of central sensitisation. It was also reported that neuropathic pain, as assessed by NPSI, was not associated with ENFD (measured by skin biopsy) in patients with peripheral neuropathies (47). In line with this, no associations between neuropathic pain, as measured by NPSI, and ESC levels were found in our study, which corroborated previous results (11). This could reflect the heterogeneity of neuropathic pain and its varying underlying mechanisms, as suggested in previous studies (47, 48). This is also in accordance with findings showing no associations between variables measured through skin biopsy and pain reports in patients with SFN (49). The relationship between ENFD and neuropathic pain appears to be complex; lower levels of ENFD can be associated with symptoms of neuropathic pain, especially in cases of pure SFN, but do not necessarily correlate with the intensity of pain (48).

In this study, symptoms of central sensitisation (CSI) were not associated with the severity of sudomotor dysfunction, as assessed by the ESC. This result does not corroborate previous reports of associations between autonomic deficiencies and markers and/or symptoms of central pain sensitisation in FM (9, 10). These contradictory results could be explained by the heterogeneous pathophysiological and clinical manifestations of FM, as well as by differences in patient samples. Several studies have tried to distinguish among subgroups of FM patients with phenotypes characterised by specific psychophysiological characteristics, pain intensity, and cognitive and psychosocial symptomatology (6, 39, 50, 1). For example, different subgroups of FM patients can be distinguished in terms of their somatosensory profiles (signs of central sensitisation; response to mechanical stimulation; decreased sensitivity to thermal stimuli), psychiatric comorbidities/functionality (anxiety, depression, impact of FM, sleep disorders); however, subgroups with a combination of such factors were not identified (52).

Finally, regarding the lateralisation of sudomotor dysfunction in the overall sample, lower ESC was observed in the right hand relative to the left one, and in the left foot relative to the right one, although in the latter case the differences were minimal and the effect size was small. No group differences were observed in the degree of lateralisation. These results are congruent with those of Pickering *et al*. (8) and suggest non-symmetrical sudomotor function in FM patients. Studies measuring SC typically reported greater SC responses in the non-dominant than dominant hand (53). Significant physiological asymmetries in surface electromyography of the trapeziums muscle, skin temperature (from the second fingers of the right and left hand) and SC (from the palms of the right and left hands) between the right and left sides of the body in FM patients have also previously been observed (54). Previous studies of lateralisation of SC and temperature observed lower values in the dominant hand relative to the non-dominant one (55). Lateralisation of sympathetic brain control to the right hemisphere has been suggested (56), which is in line with the greater ESC found in the left than right hand in our study. Similar to autonomic control, the evidence points to asym-

metry in cerebral control of pain processing, with a lateralisation to the right hemisphere that favours greater perceived pain in the left hemibody (56).

Regarding the limitations of our study, it would have been useful to assess SFN using direct methods like skin biopsy, which would have allowed for better characterisation of the subgroups with and without dysfunction in small nerve fibres. Furthermore, a larger sample of patients would have allowed us to identify and analyse different subgroups of patients (*e.g.* differing in the degree of depression), and thus to draw more robust conclusions. Future studies including a control group composed of patients with clinical depression and free from chronic pain should elucidate whether reduced ESC is inherent to FM or a secondary manifestation of the comorbid depression that usually accompanies the disease.

In conclusion, after excluding patients using tricyclic antidepressants and those suffering from class II obesity, as well as controlling for BMI, ESC was found to be lower in patients with FM than in healthy individuals, with the results indicating moderate-to-severe sudomotor dysfunction in approximately half of the patients. This supports the fundamental pathophysiological heterogeneity of FM phenotypes. However, sudomotor dysfunction was not associated with the clinical severity of the disease. This suggests that levels of peripheral neuropathy commonly observed in FM do not play a major role in determining the patient's clinical status. ESC was only associated with depression levels, which calls into question whether the ESC deficiencies are inherent to FM or secondary to comorbid depression. Future studies using more direct methods to assess SFN, and including FM patients suffering and not suffering from depression as well as patients with depression but free from chronic pain, are required to deepen our understanding of this issue.

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