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Associations among serum VEGF and CGRP levels with the peripheral vascular blood flow of the skin of the hands in women with Fibromyalgia

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ABSTRACT

Background: Fibromyalgia (FM) is a long-term condition of unknown physiopathology, whose hallmark symptoms are diffuse musculoskeletal chronic pain and fatigue.
Objectives: We aimed to analyze the associations among serum vascular endothelial growth factor (VEGF) and calcitonin gene-related peptide (CGRP) levels with the peripheral temperature of the skin of both hands and the core body temperature in patients with FM and healthy controls.
Methods: We conducted a case-control observational study with fifty-three women diagnosed with FM and twenty-four healthy women. VEGF and CGRP levels were spectrophotometrically analyzed in serum by enzyme-linked immunosorbent assay. We used an infrared thermography camera to assess the peripheral temperature of the skin of the dorsal thumb, index, middle, ring, and pinkie fingertips and dorsal centre as well as the palm thumb, index, middle, ring, and pinkie fingertips, palm centre and thenar and hypothenar eminences of both hands and an infrared thermographic scanner to record the tympanic membrane and axillary temperature.
Results: Linear regression analysis adjusting for age, menopause status, and body mass index showed that serum VEGF levels were positively associated with the maximum ($\beta = 65.942$, 95% CI [4.100,127.784], $p = 0.037$), minimum ($\beta = 59.216$, 95% CI [1.455,116.976], $p = 0.045$), and mean ($\beta = 66.923$, 95% CI [3.142,130.705], $p = 0.040$) temperature of the thenar eminence of the non-dominant hand, as well as with the maximum temperature of the hypothenar eminence of the non-dominant hand ($\beta = 63.607$, 95% CI [3.468,123.747], $p = 0.039$) in women diagnosed with FM.
Conclusions: Mild associations were observed between serum VEGF levels and the peripheral temperature of the skin in hand areas in patients with FM; therefore, it is not possible to establish a clear relationship between this vasoactive molecule and vasodilation of the hands in these patients.

1. Introduction

Fibromyalgia (FM) is a complex syndrome commonly characterized by widespread musculoskeletal chronic pain, which may also be accompanied by additional symptoms as paraesthesias or sensory deficits (neurologic symptoms), headaches or nausea (somatic symptoms), chronic fatigue or insomnia (comorbid symptoms), memory impairments or concentration difficulties (cognitive symptoms), and sensitivity to bright lights or loud sounds (sensitivity hyperresponsiveness symptoms) (Bair and Krebs, 2020; Wolfe et al., 2016). The prevalence of FM on average is 2.7% in the general world population, 2.64% in the Europe region, and 2.40% in the Spanish population, mainly affecting women (Cabo-Meseguer et al., 2017; Queiroz, 2013). FM usually manifests between 30 and 50 years of age in the worldwide population, and between 40 and 49 years of age in the Spanish population (Cabo-Meseguer et al., 2017; Gayà et al., 2020).

The physiopathology of FM is still unknown. The prevailing hypothesis suggests that peripheral and central sensitization could explain the diffuse chronic pain and altered nociception characteristic of this population (Chinn et al., 2016; Sluka and Clauw, 2016). In addition,

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other factors have been proposed to play a role in the physiopathology of FM such as vascular alterations, neurogenic and inflammatory processes, and genetic influence, among others (Albrecht et al., 2013; Morf et al., 2005; Peck et al., 2020). Previous studies have shown microvascular circulation impairments and reduced blood flow and oxygenation to the musculoskeletal deep tissue caused by changes in the sensory innervation to the arteriovenous anastomoses (AVAs) in the skin of patients with FM (Albrecht et al., 2013; Morf et al., 2005). AVAs are direct connections between small arterioles and venules located in the depth of glabrous skin of the dorsal and palm of the hands, whose main role is to transport the heat from the human body's core to peripheral skin regions (Walløe, 2016). To this regard, Albrecht et al. (2013) found an altered neural vasoregulation at the hands AVAs in a population of women diagnosed with FM, which was characterized by an excessive peptidergic sensory innervation. This sensory overrepresentation stimulates dermal peptidergic sensory fibers, activating the local "axon-reflex" and releasing vasoactive neuropeptides and inflammatory markers at the blood flow, which can modify the mechanisms that operate among capillaries and peripheral arterioles, thus altering both the peripheral blood microcirculation and thermogenesis process in patients with FM (Albrecht et al., 2013; Walløe, 2016).

Vascular endothelial growth factor (VEGF), also known as vascular permeability factor, exerts important roles in the circulatory system, since it stimulates blood vessels growth, endothelial cell survival, and angiogenesis, and regulates the blood microcirculation through the activation of its receptors, VEGFR-1 and VEGFR-2 (Berse et al., 1992). VEGF may also play a role in the vasodilation via nitric oxide (NO)-dependent pathways (Connolly, 1991; Hoeben et al., 2004). There are very few studies available that have examined VEGF in FM patients, showing contradictory results (Blanco et al., 2010; Karadağ et al., 2019; Kim et al., 2010).

Calcitonin gene-related peptide (CGRP) is a neuropeptide widely distributed in the brain, gut and perivascular nerves that has important biological effects on gastrointestinal, endocrine, and central nervous system (Russell et al., 2014). CGRP exerts both neurotransmitter and vascular functions. It is a potent endogenous vasodilator associated to increased skin temperature, vasodilation, and sweating functions (Brain and Grant, 2004; Oliveira et al., 2018). CGRP is also a neurotransmitter involved in central and peripheral sensitization, which is the main hypothesis on the physiopathology of FM, exerting pro-nociceptive effects (Iyengar et al., 2017; Russell et al., 2014). To our knowledge, only one study has evaluated CGRP levels in patients with FM, finding higher levels in patients in comparison to controls (Korucu et al., 2020).

On the other hand, thermography is a novel tool to assess vascular reactivity since provides an optimal relationship between peripheral blood flow changes and the thermal properties of the skin (Fujimasa et al., 2000; Sagaidachnyi et al., 2014). Thermography is based on the "heat transfer theory" that proposes that higher heat in a body region is related to increased blood flow and that, conversely, higher cold in a body region represents a decreased blood flow (Sagaidachnyi et al., 2017).

The scarce studies on VEGF and CGRP in FM indicate the necessity for further research in this field to better understand the involvement of these vasoactive molecules in the physiopathology of FM. Given that both VEGF and CGRP exert important roles in the microvascular system, the present study aims to analyze the associations among serum VEGF and CGRP levels with both the peripheral temperature of the skin at the dorsal and palmar sites of the hands and the core body temperature in a population of women with FM and in healthy controls.

2. Material and methods

2.1. Design and study population

A case-control observational study was conducted between September 2019 and March 2020. The Ethics Committee of Research of the University Hospital of Granada (Granada, Spain) approved the present study (approval number: 1718-N-18), which was conducted in compliance with the Declaration of Helsinki (modified in 2013) of the World Medical Association (WMA). Fifty-three women diagnosed with FM, recruited from both the Association of Fibromyalgia of Granada (AGRAFIM, Spain) and the Association of Fibromyalgia of Jaén (AFIXA, Spain), and twenty-four healthy women, recruited from the patients' relatives, friends and colleagues and from the Faculty of Health Sciences staff (University of Granada, Spain) were enrolled. The inclusion criteria for the patients were: 1) aged between 30 and 70 years; 2) previous diagnosis of FM from a rheumatology specialist of the Public Health System of Andalucía (Spain) and in accordance to the classification criteria for FM of the American College of Rheumatology, revised in 2016 (Wolfe et al., 2016). The inclusion criteria for the healthy women were: 1) aged between 30 and 70 years, and 2) absence of FM diagnosis. The exclusion criteria for both groups were: 1) male sex; 2) hepatic, cardiac or renal disease; 3) rheumatic diseases; 4) hypertension/hypotension or diabetes mellitus; 5) any acute or painful illness; 6) skin disorders; 7) severe physical disability; 8) psychiatric illness; 9) neurological diseases; 10) cancer; 11) previous history of surgery; 12) pregnancy or lactation; and 13) use of corticosteroids, anticoagulants, oestrogens, vasoactive drugs, contraceptives, or agonist/antagonist opioid receptors. We selected participants based on the inclusion and exclusion criteria proposed and according to the demographic and clinical data they provided in their first visit to our laboratory of the University of Granada (Spain). Each participant provided her demographic and clinical data by means of an interview and filling out a questionnaire regarding age, height, weight, age of onset of menopause, menopause status, dominant hand, and medical history. The same clinician helped all the participants to fill out the questionnaire. The informed consent was signed by all the participants.

2.2. Measures

In a second visit to our laboratory, all the measures were taken. The visit lasted 60 min. Prior to the second visit, the participants were instructed to wear comfortable clothing and to avoid wearing watches, bracelets and rings in the hands. In addition, 2 h before the visit, all the participants were asked to refrain ingesting vasoactive substances such as alcohol, caffeine, tea or nicotine (smoking).

2.2.1. Thermographic imaging procedure

We obtained information on peripheral vascular blood flow of the hands by recording changes in the peripheral temperature of the skin by using an infrared thermography (IRT) camera (FLIR B335, FLIR Systems AB, Täby, Sweden). The main characteristics of the FLIR B335 camera are a resolution of 320 × 240 pixels, a frequency of 30 Hz, a temperature range from −20 to 120 °C, an accuracy of ±2 °C or 2% of reading and a thermal sensitivity of 0.05 °C. Ambient temperature of the camera was set to 23 °C and emissivity to 0.98, since human skin shows an emissivity range between 0.96 and 0.99 (Ring and Ammer, 2000; Sanchez-Marin et al., 2009). FLIR systems have been used to analyze the skin surface temperature in several populations with chronic diseases such as FM (Sampere-Rubio et al., 2021), chronic neck pain (Girasol et al., 2018), and Raynaud's phenomenon (Scolnik et al., 2016).

Thermographic imaging was conducted in accordance to the recommendations of the European Association of Thermology, and thermograms were collected by the same clinician. For thermalization, the participants stayed in a sitting position in a room with a temperature of 24 ± 1 °C for at least 20 min before the evaluation. The image was taken from the distal phalanges to the wrist both at the dorsal and the palmar sites of both hands, with the patient' hands positioned on a table with splayed fingers resting (Ring and Ammer, 2012). The distance between the hands and the camera was 60 cm (Lim et al., 2014). Then, the maximum, minimum and mean temperatures of each area in both hands were calculated using the FLIR Tools Software. The camera software

presents a "rainbow" colorimetric palette formed by 85–100 colours, with a temperature range of 10 °C as recommended by previous published protocols (Ring and Ammer, 2012). The thermogram provides different colours where white and red indicate the hottest areas, orange, yellow and green the mid-range areas, and blue and black for coldest areas. Moreover, the temperature scale was automatically adjusted to the thermal content of the image. The analysis of the skin surface temperature was conducted through a circle or ellipse at the centre of each dorsal and palmar fingertip (diameter 10 × 10 mm), at the dorsal and palmar centre of each hand (diameter 20 × 20 mm), at the thenar eminence of each hand (diameter 38 × 72 mm), and at the hypothenar eminence of each hand (diameter 31 × 75 mm). Thermographic imaging was performed always in the morning to avoid the effects of circadian rhythm on skin temperature (Chierighini Salamunes et al., 2017). Fig. 1 shows the thermographic imaging procedure.

2.2.2. Core body temperature

A hand-held infrared thermographic scanner (Infrared Dermal Thermometers, Exergen, DT-1001-LN) was used in the external auditory canal of the participants to record the core body temperature. This is a simple and non-invasive method that reflects with absolute accuracy the central temperature taken from the tympanic membrane due to the existing association between the tympanic artery and the hypothalamus, which regulates the homeostatic control of the body temperature (Gasim et al., 2013). The temperature of the axillary region was also recorded given its reliability to estimate the core body temperature (Lodha et al., 2000). However, its sensitivity and specificity for reflecting the core body temperature is lower than those of the measurement of the tympanic temperature (Asadian et al., 2016; Jahanpour et al., 2015). The DT-1001-LN presents a clinical accuracy of 0.1 °C with a temperature range from 18 to 43 °C. We made three measurements at the ear or axilla coinciding with the dominant side of the patient's body (that is, if the patient was right-handed, the temperature was measured in the right ear or axilla and vice versa) to obtain the average tympanic or axillary temperature, respectively. We also calculated the "difference tympanic temperature" and the "difference axillary temperature" as the difference between the tympanic or axillary temperature and the mean temperature of the hypothenar eminence of both hands (dominant and non-dominant).

2.2.3. Blood collection and serum VEGF and CGRP levels measurement

The blood was drawn just after taking the temperature measurements, all of which were performed in the same room. In addition, blood samples were collected by the same nurse and at the same time of day in order to avoid circadian variations in VEGF and CGRP levels. Blood samples were taken from the median cephalic vein by venipuncture and collected into an anticoagulant-free tube. After blood clotted for 30 min at room temperature, the tubes were centrifuged at 3.500 rpm (Avanti J-30I; Beckman Coulter, California, USA) for 5 mint at 4 °C to obtain serum samples.

Human VEGF and CGRP levels were measured spectrophotometrically by enzyme-linked immunosorbent assay (ELISA) in serum samples according to the instructions of the manufacturer (Human Vascular Endothelial Cell Growth Factor A ELISA Kit, Elabscience, Reference: E-EL-H0111; and CGRP (human) ELISA kit, Bertin Bioreagent, Reference: #A05481.96 wells, respectively). ELISA is an immunological assay used to quantify a ligand (commonly a protein) in biological samples. The assay uses an antibody, bound to a solid support (generally 96-well

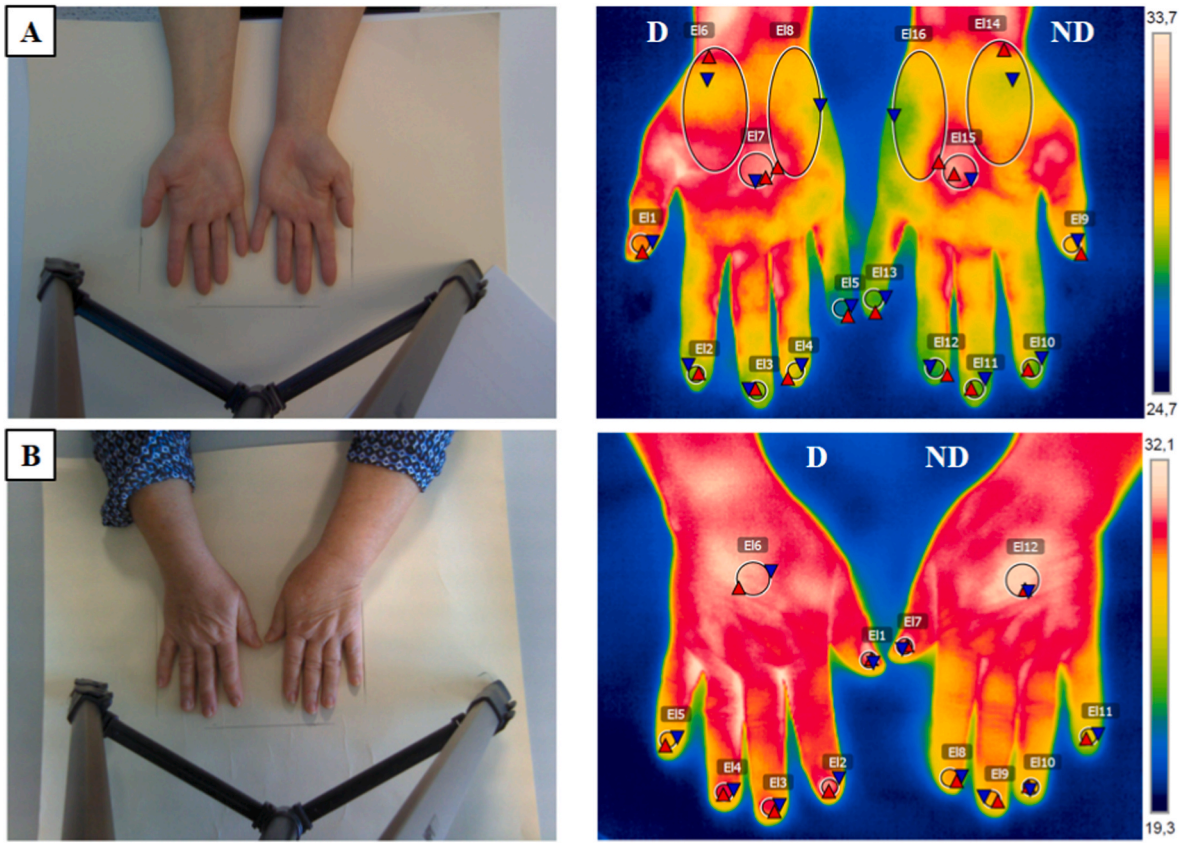

Fig. 1. Thermographic imaging procedure of the hands in a woman with Fibromyalgia and in a healthy woman. (A) Thermographic image of the palms of the hands of a woman with Fibromyalgia (El1 and El9 = thumb finger; El2 and El10 = index finger; El3 and El11 = middle finger; El4 and El12 = ring finger; El5 and El13 = pinkie finger; El6 and El14 = thenar eminence; El7 and El15 = palmar centre; El8 and El16 = hipothenar eminence) (B) Thermographic image of the dorsal area of the hands of a healthy woman (El1 and El7 = thumb finger; El2 and El8 = index finger; El3 and El9 = middle finger; El4 and El10 = ring finger; El5 and El11 = pinkie finger; El6 and El12 = dorsal centre). D = dominant hand, ND = non-dominant hand.

plates), directed against the protein to be measured. The sample containing the ligand is added and it binds the specific antibody. For the detection, an enzyme-labeled antibody against the ligand is added, which is combined with the ligand. After the enzyme's substrate is added, a colored product that can be quantified is formed.

2.2.4. Questionnaires

The questionnaires were filled out by the participants just after the blood was drawn. The Spanish version of the Revised Fibromyalgia Impact Questionnaire (FIQ-R) is a 21-item questionnaire that assesses the severity of FM by analyzing the difficulty in performing daily activities, the overall impact of the disease, and the intensity of the FM symptoms in the last 7 days. The total score ranges from 0 to 100 and the cut-off points established for the severity of FM are as follows: FIQ-R $\leq$ 30 reflects no severity, FIQ-R $>$ 30 and $\leq$45 reflects mild severity, FIQ-R $>$ 46 and $\leq$65 reflects moderate severity, and FIQ-R $>$ 65 reflects high severity (Salgueiro et al., 2013). A visual analog scale (VAS), consisting of a 100 mm-long horizontal line, was used to measure musculoskeletal pain (Marques et al., 2008). The VAS was completed by all study participants, while the FIQ-R was completed only by patients with FM.

2.3. Statistical analysis

The Ene 3.0 software (GlaxoSmithKline, Rockbille, MA, USA) was used to estimate the sample size. Taking into account the previous results of CGRP-like activity levels in chronic pain patients (Lindh et al., 1999) and of serum VEGF levels in patients with rheumatoid arthritis (Ballara et al., 2001), it is necessary to include a minimum of 19 or 7 subjects per group respectively to provide a power of 80% and an alpha level (α) of 0.05.

The data were analyzed using the SPSS Statistics Version© 24 software for Windows (IBM Corporation, Armonk, NY, USA). The normality of the variables was tested through the Kolmogorov-Smirnov test (α-value = 0.05). To compare data between FM and control groups, we used an unpaired Student's t-test with a 95% confidence interval (95% CI; $\alpha = 0.05$) for continuous variables and the chi-square test (χ^2) for categorical variables. We performed a linear regression analysis adjusting for age, menopause status, and body mass index (BMI) to test the associations among serum VEGF and CGRP levels and the peripheral temperature of the skin of both hands as well as the tympanic and axillary temperatures in both study groups. These covariates were included because they can reportedly affect FM symptoms (Çakit et al., 2018; Sarzi-Puttini et al., 2020; Sturgeon et al., 2014; Watt, 2018). The results were reported as beta estimate (β) with 95% CI and p-value. Statistical significance was set at $p < 0.05$.

3. Results

Fig. 2 depicts the flow diagram of the selection of the participants throughout the study. The demographic data, biological parameters, and central and peripheral temperatures are detailed in Table 1. Women with FM presented a mean VAS score of 74.72 $\pm$ 16.24 and a mean FIQ-R score of 73.71 $\pm$ 13.26, indicating that patients were severely affected by this syndrome. Patients with FM showed significantly higher maximum, minimum and mean temperatures at all areas evaluated at the dorsal and palmar sites of both hands than the healthy women ($p <$ 0.001). The VAS score of women with FM was significantly higher than that of the controls ($p < 0.001$). No significant differences were found between patients with FM and healthy women for age, BMI, serum VEGF and CGRP levels, tympanic temperature and axillary temperature, although differences between groups approached statistical significance for serum CGRP levels (p = 0.078).

Tables 2–5 show the associations among serum VEGF and CGRP levels with peripheral temperature of the skin of both hands and the core body temperature, expressed as β estimates and 95% CI. The linear regression analysis adjusting for age, menopause status and BMI showed that serum VEGF levels were significantly associated with the maximum temperature of the thenar eminence of the non-dominant hand ($\beta =$

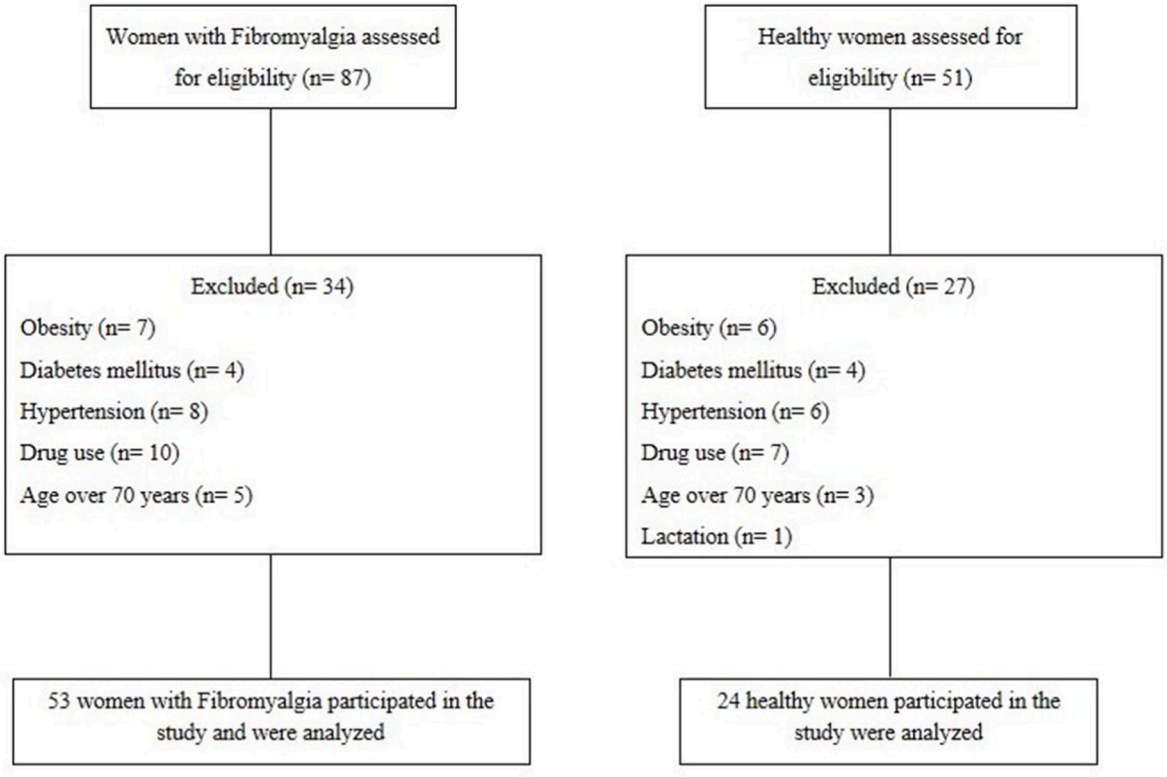

Fig. 2. Flow diagram of the screening of patients for study participation.

Table 1
Summary of demographic data, biological parameters, and central and peripheral temperatures in women with Fibromyalgia and healthy women.

Variable		Women with FM (n = 53)	Healthy women (n = 24)	
		Mean ± SD/ Frequency (%)	Mean ± SD/ Frequency (%)	*P*-value
Age (years)		55.40 ± 6.64	53.33 ± 4.68	0.174
Height (cm)		158.45 ± 5.53	160.08 ± 5.45	0.233
Weight (kg)		68.27 ± 9.85	66.19 ± 10.65	0.405
BMI (kg/cm^2)		27.93 ± 6.03	25.87 ± 4.36	0.137
Age of onset of menopause (years)		48.15 ± 6.77	49.86 ± 4.13	0.382
Duration of FM (years)		10.33 ± 7.23	–	–
Menopause status				
Pre-menopausal		13 (24.53)	13 (54.16)	0.011*
Post-menopausal		40 (75.47)	11 (45.84)	
FIQ-R				
FIQ-R.1		19.91 ± 5.19	–	–
FIQ-R.2		14.13 ± 4.52	–	–
FIQ-R.3		39.68 ± 5.82	–	–
Total score		73.71 ± 13.26	–	–
VAS (mm)		74.72 ± 16.24	12.17 ± 21.94	<0.001*
VEGF (pg/mL)		348.07 ± 261.96	364.74 ± 247.60	0.708
CGRP (pg/mL)		45.36 ± 36.54	35.21 ± 3.37	0.078
Tympanic temperature °C		36.08 ± 0.74	35.95 ± 0.59	0.450
Axillary temperature °C		35.47 ± 0.71	35.47 ± 0.43	0.992
Temperature at dorsal sites of both hands				
Thumb fingertip (°C)	**D**	31.17 ± 2.54	30.82 ± 3.49	0.001*
	ND	33.09 ± 2.53	30.83 ± 3.21	0.001*
Index fingertip (°C)	**D**	32.69 ± 2.98	30.13 ± 3.87	0.002*
	ND	32.52 ± 2.86	30.03 ± 3.50	0.002*
Middle fingertip (°C)	**D**	32.55 ± 2.99	29.83 ± 3.97	0.002*
	ND	32.33 ± 2.96	29.86 ± 3.33	0.002*
Ring fingertip (°C)	**D**	32.64 ± 2.88	29.72 ± 3.99	0.001*
	ND	32.18 ± 2.90	29.69 ± 3.48	0.002*
Pinkie fingertip (°C)	**D**	32.33 ± 2.78	29.31 ± 3.95	<0.001*
	ND	32.03 ± 2.80	29.14 ± 3.48	<0.001*
Dorsal centre (°C)	**D**	32.79 ± 1.50	31.30 ± 1.62	<0.001*
	ND	32.60 ± 1.56	30.98 ± 1.48	<0.001*
Temperature at palmar sites of both hands				
Thumb fingertip (°C)	**D**	31.98 ± 2.49	29.96 ± 3.30	0.004*
	ND	31.78 ± 2.50	29.85 ± 3.16	0.006*
Index fingertip (°C)	**D**	31.70 ± 2.91	29.40 ± 3.95	0.006*
	ND	31.31 ± 2.86	29.06 ± 3.63	0.005*
Middle fingertip (°C)	**D**	31.26 ± 2.97	28.81 ± 4.00	0.004*
	ND	31.01 ± 2.92	28.71 ± 3.48	0.004*
Ring fingertip (°C)	**D**	31.14 ± 2.88	28.65 ± 3.98	0.003*
	ND	31.01 ± 2.98	28.65 ± 3.71	0.004*
Pinkie fingertip (°C)	**D**	31.33 ± 2.90	28.69 ± 4.09	0.002*
	ND	31.14 ± 2.90	28.70 ± 3.90	0.003*
Palm centre (°C)	**D**	33.93 ± 1.15	32.49 ± 1.41	<0.001*
	ND	33.83 ± 1.18	32.32 ± 1.15	<0.001*
Thenar eminence (°C)	**D**	32.75 ± 1.22	31.49 ± 1.25	<0.001*
	ND	32.61 ± 1.18	31.29 ± 1.15	<0.001*
Hypothenar eminence (°C)	**D**	32.56 ± 1.52	31.07 ± 1.77	<0.001*
	ND	32.37 ± 1.51	30.91 ± 1.49	<0.001*

* Significance level $P < 0.05$.
Note. Data are expressed as mean ± standard deviation (SD) for quantitative variables and as frequency (%) for qualitative variables. Abbreviations. FM: Fibromyalgia; FIQ-R: Revised Fibromyalgia Impact Questionnaire; FIQ-R.1: activity level of the FIQ-R; FIQ-R.2: overall impact of the FIQ-R; FIQ-R.3: intensity of symptoms of the FIQ-R; VAS: visual analog scale; BMI: body mass index; VEGF: vascular endothelial growth factor; CGRP: calcitonin gene-related peptide; °C: Celsius degree; D: dominant; ND: non-dominant.

65.942, 95% CI [4.100,127.784], $p = 0.037$), with the minimum temperature of the thenar eminence of the non-dominant hand ($\beta = 59.216$, 95% CI [1.455,116.976], $p = 0.045$), with the mean temperature of the thenar eminence of the non-dominant hand ($\beta = 66.923$, 95% CI [3.142,130.705], $p = 0.040$), as well as with the maximum temperature of the hypothenar eminence of the non-dominant hand ($\beta = 63.607$, 95% CI [3.468,123.747], $p = 0.039$) in women with FM. There were no significant interactions between VEGF levels and the peripheral and central temperatures in healthy women. Similarly, no significant differences were found between serum CGRP levels and the temperatures recorded in patients and controls. However, several associations approached statistical significance. That is, serum VEGF levels were correlated with the minimum temperature of the dorsal ring fingertip of the non-dominant hand ($\beta = 25.494$, 95% CI [−1.393,52.380], $p = 0.063$), with the minimum temperature of the thumb fingertip of the palmar non-dominant hand ($\beta = 25.575$, 95% CI [−4.310,55.461], $p = 0.092$), with the maximum ($\beta = 62.492$, 95% CI [−3.172,128.156], $p = 0.062$), minimum ($\beta = 50.421$, 95% CI [−7.585,108.426], $p = 0.087$), and mean ($\beta = 60.274$, 95% CI [−2.939,123.487], $p = 0.061$) temperature of the palmar centre of the non-dominant hand, with the minimum temperature of the thenar eminence of the dominant hand ($\beta = 52.081$, 95% CI [−2.688,106.850], $p = 0.062$), and with the difference between the axillary temperature and the mean temperature of the hypothenar eminence of the dominant hand ($\beta = -54.449$, 95% CI [−117.059,8.162], $p = 0.086$) and non-dominant hand ($\beta = -51.421$, 95% CI [−107.243,4.401], $p = 0.070$) in women with FM. Also, serum VEGF levels were associated with the minimum temperature of the hypothenar eminence of the non-dominant hand ($\beta = 51.009$, 95% CI [−1.160,103.358], $p = 0.055$) and with the tympanic temperature ($\beta = 169.515$, 95% CI [−5.118,344.148], $p = 0.056$) in healthy women.

4. Discussion

The physiopathological mechanisms underlying FM are not yet established, which makes the diagnosis, management and treatment of patients difficult. Alterations in both microvascular circulation and blood flow have been reported in the skin of patients with FM (Albrecht et al., 2013; Morf et al., 2005), although the mechanisms by which these alterations occur are unknown. VEGF and CGRP are molecules with vasodilator effects, which could alter the skin microvasculature and blood perfusion, thereby affecting the peripheral microcirculation blood flow and temperature. The present study aims at searching for associations between serum VEGF and CGRP levels and peripheral temperature of the skin of the hands and core body temperature in patients with FM and healthy controls.

Our results have shown that women with FM had higher temperature at all areas evaluated at the dorsal and palmar sites of both hands than the controls, which could be related to an altered peripheral vascular blood flow in the hands of these patients. We obtained similar results in a previous study in which we investigated the relationship between the vasodilator molecule NO and the peripheral and central temperatures in women with FM and healthy women (Aguilar-Ferrándiz et al., 2021). To our knowledge, there are no previous studies analyzing these temperatures in FM patients compared to controls. However, a clinical trial conducted by Pickering and colleagues in fifty women with FM and fifty matched healthy women evaluated the electrochemical skin conductance in the dominant hand. The authors observed that warm detection thresholds happened at later temperature in FM patients compared to healthy controls (34.8 ± 0.7 °C and 33.6 ± 0.6 °C, respectively) (Pickering et al., 2020). Supporting the hypothesis that higher peripheral temperature of the skin of the hands in women with FM may be related to peripheral microvascular alterations, several studies have shown morphology capillaries disorders and blood microcirculation alterations in patients with FM (Choi and Kim, 2015; Morf et al., 2005). In line, it has been reported that a dysfunction of the Autonomic Nervous System (ANS) might alter the microcirculation and sweating functions, thereby changing the body temperature (Elmas et al., 2016). Moreover, impaired ANS activity may cause an imbalance of the hand's AVAs in patients with FM, thereby affecting the thermoregulatory activity in this region (Albrecht et al., 2013). These authors, through biopsies on the hypothenar eminence skin of the hands of twenty-four women with FM, found an increased number of vasodilator sensory fibers (C and Aδ peptidergic

Table 2
Interactions between serum vascular endothelial growth factor (VEGF) levels and temperature of dorsal and palmar sites of both hands in women with Fibromyalgia and healthy controls.

Variable			Serum VEGF levels					
			Women with FM (n = 53)			Healthy women (n = 24)		
			β	95% CI	*P*-value	β	95% CI	*P*-value
Dorsal sites of both hands								
Thumb fingertip	**Maximum (°C)**	**D**	14.207	(-16.933,16.596)	0.351	3.772	(-29.394,36.938)	0.814
		ND	15.780	(-14.328,45.887)	0.297	8.136	(-26.818,43.089)	0.632
	Minimum (°C)	**D**	13.065	(-18.068,44.198)	0.403	5.313	(-28.082,38.708)	0.743
		ND	18.558	(-12.332,49.448)	0.233	15.393	(-21.377,52.163)	0.392
	Average (°C)	**D**	13.062	(-17.663,43.788)	0.397	3.760	(-28.759,36.280)	0.811
		ND	16.369	(-14.111,46.850)	0.285	9.791	(-25.955,45.538)	0.573
Index fingertip	**Maximum (°C)**	**D**	12.136	(-13.531,37.802)	0.346	1.343	(-27.886,30.573)	0.924
		ND	15.310	(-11.208,41.828)	0.251	1.309	(-31.842,34.460)	0.935
	Minimum (°C)	**D**	12.445	(-14.940,39.831)	0.365	2.710	(-27.849,33.269)	0.855
		ND	12.399	(-14.353,39.151)	0.356	4.402	(-27.644,36.449)	0.777
	Average (°C)	**D**	12.443	(-14.011,38.896)	0.349	1.475	(-28.132,31.081)	0.918
		ND	16.319	(-10.604,43.242)	0.229	2.784	(-30.399,35.967)	0.862
Middle fingertip	**Maximum (°C)**	**D**	14.441	(-11.474,40.357)	0.268	−1.003	(-29.572,27.566)	0.942
		ND	15.891	(-10.283,42.066)	0.228	4.361	(-32.132,40.853)	0.805
	Minimum (°C)	**D**	17.379	(-8.805,43.563)	0.188	1.195	(-28.240,30.629)	0.933
		ND	13.053	(-14.626,40.733)	0.347	8.870	(-26.535,44.275)	0.606
	Average (°C)	**D**	14.840	(-11.171,40.850)	0.257	−0.252	(-29.011,28.507)	0.986
		ND	16.258	(-10.136,42.651)	0.221	5.080	(-30.731,40.891)	0.770
Ring fingertip	**Maximum (°C)**	**D**	14.093	(-12.261,40.447)	0.287	−1.063	(-29.205,27.079)	0.938
		ND	16.576	(-9.386,42.539)	0.205	4.605	(-29.130,38.341)	0.778
	Minimum (°C)	**D**	15.231	(-12.233,42.695)	0.270	0.446	(-28.608,29.500)	0.975
		ND	25.494	(-1.393,52.380)	0.063	6.700	(-26.217,39.616)	0.675
	Average (°C)	**D**	14.878	(-11.945,41.701)	0.270	−0.662	(-28.953,27.629)	0.961
		ND	18.067	(-8.837,44.971)	0.183	4.990	(-28.171,38.151)	0.756
Pinkie fingertip	**Maximum (°C)**	**D**	15.823	(-11.322,42.969)	0.247	−0.096	(-28.490,28.298)	0.994
		ND	17.307	(-9.588,44.201)	0.202	8.455	(-24.524,41.433)	0.598
	Minimum (°C)	**D**	11.539	(-16.238,39.316)	0.407	2.978	(-26.280,32.237)	0.834
		ND	4.910	(-24.387,34.208)	0.737	10.056	(-29.489,49.602)	0.601
	Average (°C)	**D**	17.321	(-10.235,44.878)	0.212	0.893	(-27.713,29.499)	0.949
		ND	16.164	(-11.230,43.557)	0.241	9.246	(-23.850,42.342)	0.566
Dorsal centre	**Maximum (°C)**	**D**	32.915	(-23.418,89.248)	0.246	−0.470	(-77.925,76.986)	0.990
		ND	37.706	(-15.563,90.975)	0.161	18.324	(-68.460,105.107)	0.664
	Minimum (°C)	**D**	33.731	(-15.041,82.503)	0.171	−8.679	(-76.022,58.663)	0.790
		ND	36.384	(-11.851,84.619)	0.136	−5.677	(-80.825,69.471)	0.876
	Average (°C)	**D**	31.898	(-21.477,85.274)	0.235	−5.633	(-78.734,67.467)	0.874
		ND	36.241	(-14.889,87.370)	0.160	−0.820	(-85.312,83.672)	0.984
Palmar sites of both hands								
Thumb fingertip	**Maximum (°C)**	**D**	20.233	(-10.801,51.268)	0.196	9.664	(-24.257,43.584)	0.558
		ND	23.608	(-6.634,53.851)	0.123	18.408	(-15.397,52.213)	0.269
	Minimum (°C)	**D**	22.878	(-6.861,52.617)	0.128	8.546	(-27.147,44.239)	0.622
		ND	25.575	(-4.310,55.461)	0.092	17.560	(-20.670,55.789)	0.348
	Average (°C)	**D**	20.472	(-10.239,51.184)	0.186	9.961	(-24.229,44.152)	0.549
		ND	21.841	(-8.445,52.127)	0.153	17.627	(-17.019,52.273)	0.300
Index fingertip	**Maximum (°C)**	**D**	14.737	(-11.660,41.134)	0.267	9.505	(-18.027,37.038)	0.479
		ND	19.735	(-6.786,46.255)	0.141	8.301	(-22.660,39.262)	0.581
	Minimum (°C)	**D**	8.724	(-18.697,36.145)	0.525	8.975	(-19.561,37.511)	0.518
		ND	22.402	(-5.340,50.144)	0.111	9.524	(-22.455,41.503)	0.540
	Average (°C)	**D**	14.583	(-12.127,41.293)	0.277	9.002	(-19.091,37.094)	0.510
		ND	19.021	(-7.653,45.695)	0.158	8.758	(-22.076,39.592)	0.559
Middle fingertip	**Maximum (°C)**	**D**	14.281	(-11.703,40.266)	0.274	4.327	(-23.274,31.928)	0.746
		ND	17.985	(-8.103,44.073)	0.172	11.691	(-21.245,44.626)	0.467
	Minimum (°C)	**D**	13.274	(-13.535,40.084)	0.324	5.389	(-22.915,33.694)	0.695
		ND	16.536	(-10.372,43.445)	0.222	11.964	(-20.298,44.225)	0.447
	Average (°C)	**D**	13.733	(-12.327,39.792)	0.294	4.945	(-22.844,32.735)	0.714
		ND	16.934	(-9.297,43.166)	0.200	12.214	(-20.521,44.949)	0.444
Ring fingertip	**Maximum (°C)**	**D**	14.279	(-11.575,40.133)	0.272	4.782	(-22.618,32.181)	0.719
		ND	16.194	(-8.878,41.265)	0.200	9.164	(-20.238,38.566)	0.522
	Minimum (°C)	**D**	10.691	(-15.152,36.534)	0.409	4.569	(-23.574,32.713)	0.738
		ND	14.995	(-11.831,41.820)	0.266	12.609	(-17.559,42.778)	0.393
	Average (°C)	**D**	12.822	(-13.795,39.438)	0.337	4.560	(-23.290,32.410)	0.736
		ND	16.386	(-9.546,42.318)	0.210	11.679	(-18.286,41.643)	0.425
Pinkie fingertip	**Maximum (°C)**	**D**	14.279	(-11.596,40.155)	0.272	6.654	(-19.698,33.007)	0.603
		ND	16.233	(-9.538,42.004)	0.211	11.615	(-16.804,40.034)	0.403
	Minimum (°C)	**D**	8.263	(-19.107,35.633)	0.546	5.759	(-22.301,33.818)	0.672
		ND	11.669	(-14.571,37.908)	0.375	12.607	(-16.510,41.725)	0.376
	Average (°C)	**D**	13.355	(-13.045,39.756)	0.314	6.068	(-21.011,33.147)	0.644
		ND	16.065	(-10.263,42.392)	0.226	11.810	(-16.585,40.206)	0.395
Palm centre	**Maximum (°C)**	**D**	37.406	(-34.696,109.508)	0.302	7.177	(-69.556,83.911)	0.847

(*continued on next page*)

Table 2 (*continued*)

Variable			Serum VEGF levels					
			Women with FM (n = 53)			Healthy women (n = 24)		
			β	95% CI	*P*-value	β	95% CI	*P*-value
		ND	62.492	(-3.172,128.156)	0.062	9.533	(-91.714,110.780)	0.846
	Minimum (°C)	D	23.855	(-37.294,85.003)	0.436	8.248	(-72.284,88.780)	0.833
		ND	50.421	(-7.585,108.426)	0.087	28.800	(-65.666,123.265)	0.531
	Average (°C)	D	38.334	(-29.169,105.838)	0.259	12.983	(-66.843,92.809)	0.737
		ND	60.274	(-2.939,123.487)	0.061	0.449	(-100.252,101.151)	0.993
Thenar eminence	Maximum (°C)	D	41.542	(-28.353,111.438)	0.238	10.149	(-82.489,102.788)	0.821
		ND	65.942	(4.100,127.784)	0.037*	37.452	(-63.906,138.811)	0.449
	Minimum (°C)	D	52.081	(-2.688,106.850)	0.062	33.512	(-50.695,117.719)	0.415
		ND	59.216	(1.455,116.976)	0.045*	63.285	(-23.886,151.456)	0.145
	Average (°C)	D	48.169	(-16.115,112.454)	0.138	30.477	(-58.932,119.886)	0.484
		ND	66.923	(3.142,130.705)	0.040*	54.500	(-43.983,152.983)	0.261
Hypothenar eminence	Maximum (°C)	D	37.921	(-26.021,101.864)	0.239	2.111	(-74.092,78.313)	0.954
		ND	63.607	(3.468,123.747)	0.039*	48.284	(-48.707,145.276)	0.311
	Minimum (°C)	D	19.567	(-24.351,63.486)	0.374	22.744	(-34.212,79.701)	0.414
		ND	15.726	(-20.012,51.463)	0.380	51.099	(-1.160,103.358)	0.055
	Average (°C)	D	31.641	(-19.423,82.704)	0.219	14.737	(-48.584,78.059)	0.632
		ND	39.986	(-11.230,91.201)	0.123	45.083	(-28.138,118.304)	0.213
	Minimum (°C)	D	8.724	(-18.697,36.145)	0.525	8.975	(-19.561,37.511)	0.518
		ND	22.402	(-5.340,50.144)	0.111	9.524	(-22.455,41.503)	0.540
	Average (°C)	D	14.583	(-12.127,41.293)	0.277	9.002	(-19.091,37.094)	0.510
		ND	19.021	(-7.653,45.695)	0.158	8.758	(-22.076,39.592)	0.559
Middle fingertip	Maximum (°C)	D	14.281	(-11.703,40.266)	0.274	4.327	(-23.274,31.928)	0.746
		ND	17.985	(-8.103,44.073)	0.172	11.691	(-21.245,44.626)	0.467
	Minimum (°C)	D	13.274	(-13.535,40.084)	0.324	5.389	(-22.915,33.694)	0.695
		ND	16.536	(-10.372,43.445)	0.222	11.964	(-20.298,44.225)	0.447
	Average (°C)	D	13.733	(-12.327,39.792)	0.294	4.945	(-22.844,32.735)	0.714
		ND	16.934	(-9.297,43.166)	0.200	12.214	(-20.521,44.949)	0.444
Ring fingertip	Maximum (°C)	D	14.279	(-11.575,40.133)	0.272	4.782	(-22.618,32.181)	0.719
		ND	16.194	(-8.878,41.265)	0.200	9.164	(-20.238,38.566)	0.522
	Minimum (°C)	D	10.691	(-15.152,36.534)	0.409	4.569	(-23.574,32.713)	0.738
		ND	14.995	(-11.831,41.820)	0.266	12.609	(-17.559,42.778)	0.393
	Average (°C)	D	12.822	(-13.795,39.438)	0.337	4.560	(-23.290,32.410)	0.736
		ND	16.386	(-9.546,42.318)	0.210	11.679	(-18.286,41.643)	0.425
Pinkie fingertip	Maximum (°C)	D	14.279	(-11.596,40.155)	0.272	6.654	(-19.698,33.007)	0.603
		ND	16.233	(-9.538,42.004)	0.211	11.615	(-16.804,40.034)	0.403
	Minimum (°C)	D	8.263	(-19.107,35.633)	0.546	5.759	(-22.301,33.818)	0.672
		ND	11.669	(-14.571,37.908)	0.375	12.607	(-16.510,41.725)	0.376
	Average (°C)	D	13.355	(-13.045,39.756)	0.314	6.068	(-21.011,33.147)	0.644
		ND	16.065	(-10.263,42.392)	0.226	11.810	(-16.585,40.206)	0.395
Palm centre	Maximum (°C)	D	37.406	(-34.696,109.508)	0.302	7.177	(-69.556,83.911)	0.847
		ND	62.492	(-3.172,128.156)	0.062	9.533	(-91.714,110.780)	0.846
	Minimum (°C)	D	23.855	(-37.294,85.003)	0.436	8.248	(-72.284,88.780)	0.833
		ND	50.421	(-7.585,108.426)	0.087	28.800	(-65.666,123.265)	0.531
	Average (°C)	D	38.334	(-29.169,105.838)	0.259	12.983	(-66.843,92.809)	0.737
		ND	60.274	(-2.939,123.487)	0.061	0.449	(-100.252,101.151)	0.993
Thenar eminence	Maximum (°C)	D	41.542	(-28.353,111.438)	0.238	10.149	(-82.489,102.788)	0.821
		ND	65.942	(4.100,127.784)	0.037*	37.452	(-63.906,138.811)	0.449
	Minimum (°C)	D	52.081	(-2.688,106.850)	0.062	33.512	(-50.695,117.719)	0.415
		ND	59.216	(1.455,116.976)	0.045*	63.285	(-23.886,151.456)	0.145
	Average (°C)	D	48.169	(-16.115,112.454)	0.138	30.477	(-58.932,119.886)	0.484
		ND	66.923	(3.142,130.705)	0.040*	54.500	(-43.983,152.983)	0.261
Hypothenar eminence	Maximum (°C)	D	37.921	(-26.021,101.864)	0.239	2.111	(-74.092,78.313)	0.954
		ND	63.607	(3.468,123.747)	0.039*	48.284	(-48.707,145.276)	0.311
	Minimum (°C)	D	19.567	(-24.351,63.486)	0.374	22.744	(-34.212,79.701)	0.414
		ND	15.726	(-20.012,51.463)	0.380	51.099	(-1.160,103.358)	0.055
	Average (°C)	D	31.641	(-19.423,82.704)	0.219	14.737	(-48.584,78.059)	0.632
		ND	39.986	(-11.230,91.201)	0.123	45.083	(-28.138,118.304)	0.213

* Significance level $P < 0.05$.

Note. FM: Fibromyalgia; Beta (β): regression coefficient adjusted for age, menopause status and body mass index; 95% CI: 95% confidence interval; VEGF: vascular endothelial growth factor; °C: Celsius degree; D: dominant; ND: non-dominant.

fibers) together with a decreased number of noradrenergic sympathetic fibers (Albrecht et al., 2013), leading to the release of vasodilator neuropeptides such as substance P, CGRP or VEGF. The release of these neuropeptides at the blood flow may affect the peripheral blood vessels, thus leading to local vasodilation in the peripheral skin that could be responsible, at least in part, from the higher temperature of hands of FM patients that we have found in the present study. On the other hand, it has been reported that there is a high prevalence of small fibers neuropathy in FM (de Tommaso et al., 2022; Grayston et al., 2019). Although neurological disorders such as peripheral neuropathy were an exclusion criterion in our study, the possibility that they had not been adequately diagnosed in our FM patients cannot be ruled out. The Aδ and C small fibers of the Peripheral Nervous System relay pain and thermal perception (cold and heat), and also innervate sweat glands (Pickering et al., 2020). Damage to these fibers ultimately leads to temperature dysregulation and altered function of the small blood vessels (Grayston et al., 2019). In this way, this neurogenic microvasculopathy could also explain, at least partially, the altered hand

Table 3
Interactions between serum calcitonin gene-related peptide (CGRP) levels and temperature of dorsal and palmar sites of both hands in women with Fibromyalgia and healthy controls.

Variable			Serum CGRP levels					
			Women with FM (n = 53)			Healthy women (n = 24)		
			β	95% CI	*P*-value	β	95% CI	*P*-value
Dorsal sites of both hands								
Thumb fingertip	**Maximum (°C)**	**D**	0.487	(-3.863,4.837)	0.823	0.049	(-0.423,0.522)	0.828
		ND	−0.328	(-4.657,4.001)	0.879	0.065	(-0.435,0.566)	0.786
	Minimum (°C)	**D**	1.029	(-3.456,5.514)	0.646	0.089	(-0.389,0.566)	0.700
		ND	−0.532	(-5.011,3.946)	0.812	−0.032	(-0.569,0.506)	0.903
	Average (°C)	**D**	0.462	(-3.946,4.870)	0.834	0.067	(-0.396,0.530)	0.764
		ND	−0.406	(-4.798,3.986)	0.853	0.061	(-0.455,0.576)	0.807
Index fingertip	**Maximum (°C)**	**D**	0.277	(-3.421,3.975)	0.881	0.030	(-0.387,0.447)	0.882
		ND	−0.290	(-4.114,3.534)	0.879	0.163	(-0.312,0.637)	0.479
	Minimum (°C)	**D**	0.792	(-3.151,4.736)	0.687	0.036	(-0.405,0.478)	0.864
		ND	−0.975	(-4.812,2.862)	0.611	0.152	(-0.309,0.612)	0.496
	Average (°C)	**D**	0.402	(-3.408,4.211)	0.833	0.030	(-0.393,0.453)	0.882
		ND	−0.440	(-4.328,3.448)	0.821	0.160	(-0.315,0.635)	0.486
Middle fingertip	**Maximum (°C)**	**D**	0.209	(-3.536,3.953)	0.911	0.041	(-0.370,0.452)	0.835
		ND	−0.293	(-4.080,3.495)	0.877	0.162	(-0.363,0.687)	0.524
	Minimum (°C)	**D**	0.497	(-3.319,4.312)	0.794	0.058	(-0.365,0.482)	0.774
		ND	−0.537	(-4.527,3.452)	0.787	0.037	(-0.479,0.553)	0.881
	Average (°C)	**D**	0.340	(-3.420,4.100)	0.856	0.041	(-0.372,0.454)	0.836
		ND	−0.399	(-4.222,3.424)	0.834	0.140	(-0.377,0.656)	0.576
Ring fingertip	**Maximum (°C)**	**D**	0.031	(-3.763,3.824)	0.987	0.032	(-0.373,0.437)	0.869
		ND	0.811	(-2.945,4.567)	0.666	0.135	(-0.347,0.617)	0.561
	Minimum (°C)	**D**	0.139	(-3.845,4.123)	0.944	0.052	(-0.367,0.470)	0.798
		ND	1.585	(-2.391,5.560)	0.426	0.157	(-0.312,0.625)	0.490
	Average (°C)	**D**	−0.004	(-3.873,3.866)	0.999	0.030	(-0.377,0.437)	0.877
		ND	0.992	(-2.909,4.893)	0.611	0.141	(-0.332,0.614)	0.537
Pinkie fingertip	**Maximum (°C)**	**D**	−0.605	(-4.516,3.307)	0.757	0.081	(-0.338,0.499)	0.690
		ND	0.607	(-3.286,4.500)	0.755	0.161	(-0.312,0.634)	0.483
	Minimum (°C)	**D**	−0.537	(-4.505,3.432)	0.787	0.077	(-0.351,0.505)	0.710
		ND	0.537	(-3.658,4.732)	0.798	0.025	(-0.557,0.608)	0.928
	Average (°C)	**D**	−0.739	(-4.719,3.241)	0.710	0.073	(-0.347,0.493)	0.717
		ND	0.619	(-3.338,4.577)	0.754	0.147	(-0.330,0.624)	0.524
Dorsal centre	**Maximum (°C)**	**D**	−1.165	(-9.251,6.920)	0.773	−0.113	(-1.278,1.053)	0.841
		ND	−0.024	(-7.755,7.706)	0.995	−0.094	(-1.422,1.235)	0.883
	Minimum (°C)	**D**	−0.907	(-7.693,6.149)	0.797	−0.082	(-1.059,0.896)	0.862
		ND	−0.333	(-7.385,6.719)	0.925	0.009	(-1.065,1.082)	0.987
	Average (°C)	**D**	−1.010	(-8.680,6.660)	0.792	−0.079	(-1.154,0.996)	0.878
		ND	−0.140	(-7.570,7.291)	0.970	−0.016	(-1.250,1.218)	0.978
Palmar sites of both hands								
Thumb fingertip	**Maximum (°C)**	**D**	0.630	(-3.924,5.183)	0.782	0.173	(-0.317,0.663)	0.465
		ND	−0.551	(-5.010,3.909)	0.805	0.085	(-0.419,0.590)	0.726
	Minimum (°C)	**D**	1.206	(-3.166,5.578)	0.581	0.059	(-0.456,0.574)	0.812
		ND	0.451	(-3.956,4.859)	0.838	0.232	(-0.329,0.792)	0.395
	Average (°C)	**D**	0.683	(-3.828,5.193)	0.762	0.171	(-0.322,0.664)	0.474
		ND	−0.349	(-4.804,4.106)	0.875	0.112	(-0.403,0.626)	0.653
Index fingertip	**Maximum (°C)**	**D**	−0.012	(-3.866,3.841)	0.995	0.049	(-0.349,0.447)	0.798
		ND	−0.694	(-4.581,3.192)	0.721	0.174	(-0.279,0.627)	0.428
	Minimum (°C)	**D**	0.081	(-3.896,4.058)	0.967	0.076	(-0.336,0.488)	0.703
		ND	−0.498	(-4.617,3.621)	0.809	0.185	(-0.275,0.645)	0.409
	Average (°C)	**D**	0.030	(-3.880,3.941)	0.988	0.062	(-0.345,0.468)	0.753
		ND	−0.668	(-4.588,3.252)	0.733	0.162	(-0.289,0.613)	0.460
Middle fingertip	**Maximum (°C)**	**D**	−0.030	(-3.843,3.782)	0.987	0.088	(-0.309,0.486)	0.645
		ND	−0.925	(-4.764,2.915)	0.630	0.191	(-0.291,0.672)	0.415
	Minimum (°C)	**D**	0.175	(-3.762,4.111)	0.929	0.103	(-0.305,0.512)	0.600
		ND	−0.668	(-4.641,3.305)	0.736	0.193	(-0.273,0.660)	0.395
	Average (°C)	**D**	−0.054	(-3.856,3.749)	0.977	0.099	(-0.303,0.501)	0.611
		ND	−0.870	(-4.728,2.988)	0.652	0.196	(-0.279,0.671)	0.395
Ring fingertip	**Maximum (°C)**	**D**	−0.168	(-3.934,3.598)	0.929	0.077	(-0.319,0.473)	0.686
		ND	0.241	(-3.436,3.919)	0.895	0.150	(-0.274,0.574)	0.466
	Minimum (°C)	**D**	0.300	(-3.450,4.050)	0.873	0.091	(-0.316,0.498)	0.644
		ND	0.347	(-3.568,4.263)	0.859	0.156	(-0.284,0.596)	0.465
	Average (°C)	**D**	−0.026	(-3.911,3.858)	0.989	0.083	(-0.320,0.485)	0.670
		ND	0.292	(-3.507,4.091)	0.878	0.161	(-0.273,0.596)	0.445
Pinkie fingertip	**Maximum (°C)**	**D**	−0.585	(-4.376,3.207)	0.757	0.116	(-0.267,0.499)	0.531
		ND	0.293	(-3.472,4.059)	0.876	0.170	(-0.239,0.579)	0.393
	Minimum (°C)	**D**	−0.268	(-4.238,3.702)	0.892	0.135	(-0.258,0.527)	0.478
		ND	0.657	(-3.155,4.469)	0.730	0.163	(-0.262,0.588)	0.430
	Average (°C)	**D**	−0.523	(-4.379,3.334)	0.786	0.124	(-0.269,0.517)	0.515
		ND	0.175	(-3.683,4.034)	0.927	0.176	(-0.234,0.586)	0.337
Palm centre	**Maximum (°C)**	**D**	0.2496	(-7.876,12.868)	0.630	−0.002	(-1.080,1.076)	0.997

(*continued on next page*)

Table 3 (*continued*)

Variable			Serum CGRP levels					
			Women with FM (n = 53)			Healthy women (n = 24)		
			β	95% CI	*P*-value	β	95% CI	*P*-value
		ND	−0.369	(-10.103,9.366)	0.940	0.292	(-1.132,1.716)	0.670
	Minimum (°C)	**D**	3.372	(-5.395,12.139)	0.442	0.169	(-0.967,1.305)	0.757
		ND	0.645	(-8.016,9.307)	0.881	0.530	(-0.832,1.891)	0.423
	Average (°C)	**D**	1.764	(-7.999,11.527)	0.717	0.106	(-1.017,1.230)	0.844
		ND	0.041	(-9.419,9.500)	0.993	0.418	(-0.994,1.831)	0.540
Thenar eminence	**Maximum (°C)**	**D**	−0.875	(-10.960,9.211)	0.862	0.415	(-0.947,1.776)	0.529
		ND	−5.112	(-14.244,4.020)	0.265	0.332	(-1.143,1.808)	0.641
	Minimum (°C)	**D**	2.381	(-5.982,10.743)	0.569	0.182	(-1.033,1.398)	0.756
		ND	0.697	(-8.160,9.554)	0.875	−0.111	(-1.451,1.228)	0.863
	Average (°C)	**D**	−0.315	(-9.803,9.173)	0.947	0.399	(-0.928,1.726)	0.534
		ND	−2.234	(-11.877,7.409)	0.643	0.337	(-1.160,1.834)	0.641
Hypothenar eminence	**Maximum (°C)**	**D**	0.709	(-8.572,9.989)	0.878	−0.124	(-1.233,0.985)	0.816
		ND	−0.974	(-9.985,8.037)	0.829	0.140	(-1.284,1.564)	0.838
	Minimum (°C)	**D**	0.118	(-6.274,6.509)	0.971	0.399	(-0.457,1.256)	0.339
		ND	0.280	(-4.943,5.503)	0.914	0.251	(-0.565,1.067)	0.525
	Average (°C)	**D**	−0.449	(-7.918,7.020)	0.904	0.256	(-0.672,1.185)	0.568
		ND	0.376	(-7.241,7.993)	0.921	0.316	(-0.806,1.437)	0.560

* Significance level $P < 0.05$.
Note. FM: Fibromyalgia; Beta (β): regression coefficient adjusted for age, menopause status and body mass index; 95% CI: 95% confidence interval; CGRP: calcitonin gene-related peptide; °C: Celsius degree; D: dominant; ND: non-dominant.

Table 4
Associations between serum vascular endothelial growth factor (VEGF) levels and tympanic and axillary core temperature in women with Fibromyalgia and healthy controls.

Variable		Serum VEGF levels					
		Women with FM (n = 53)			Healthy women (n = 24)		
		β	95% CI	*P*-value	β	95% CI	*P*-value
Tympanic temperature (°C)		56.836	(-15.935,9.975)	0.645	169.515	(-5.118,344.148)	0.056
Axillary temperature (°C)		23.392	(-110.465,157.249)	0.725	27.181	(-265.230,319.592)	0.846
Difference tympanic temperature (°C)	**D**	−15.050	(-65.481,35.381)	0.550	4.338	(-63.696,72.371)	0.895
	ND	−22.124	(-72.436,28.188)	0.380	−23.792	(-109.717,62.133)	0.569
Difference axillary temperature (°C)	**D**	−54.449	(-117.059,8.162)	0.086	−39.957	(-107.287,27.374)	0.225
	ND	−51.421	(-107.243,4.401)	0.070	−60.252	(-136.242,15.738)	0.112

* Significance level $P < 0.05$.
Note. Beta (β): regression coefficient adjusted for age, menopause status and body mass index; 95% CI: 95% confidence interval; VEGF: vascular endothelial growth factor; °C: Celsius degree; D: dominant; ND: non-dominant.

Table 5
Associations between serum calcitonin gene-related peptide (CGRP) levels and tympanic and axillary core temperature in women with Fibromyalgia and healthy controls.

Variable		Serum CGRP levels					
		Women with FM (n = 53)			Healthy women (n = 24)		
		β	95% CI	*P*-value	β	95% CI	*P*-value
Tympanic temperature (°C)		7.757	(-22.972,7.457)	0.310	0.736	(-1.960,3.433)	0.572
Axillary temperature (°C)		13.559	(-7.135,34.253)	0.192	−0.505	(-5.073,4.062)	0.816
Difference tympanic temperature (°C)	**D**	−0.766	(-8.155,6.624)	0.835	−1.87	(-1.170,0.796)	0.693
	ND	−1.724	(-9.182,5.735)	0.643	−0.237	(-1.502,1.029)	0.698
Difference axillary temperature (°C)	**D**	4.825	(-5.563,15.212)	0.351	−0.309	(-1.476,0.858)	0.579
	ND	2.647	(-6.785,12.078)	0.572	−0.482	(-1.816,0.852)	0.451

* Significance level $P < 0.05$.
Note. Beta (β): regression coefficient adjusted for age, menopause status and body mass index; 95% CI: 95% confidence interval; CGRP: calcitonin gene-related peptide; °C: Celsius degree; D: dominant; ND: non-dominant.

temperatures we have found in patients with FM in comparison to controls.

The skin microvasculature can be affected by vasoactive substances with important pro-nociceptive and vasodilator effects, which have been scarcely studied in patients with FM. In this context, VEGF is a mediator of blood vessels permeability and one of those responsible for the control and adaptation of the microvascular density when the tissues demand oxygen and nutrients (Blanco et al., 2010). In the present observational study, there were no significant differences in serum VEGF levels between women with FM and healthy women. In accordance, no statistically significant differences in serum VEGF levels between groups were previously found (Karadağ et al., 2019; Kim et al., 2010). On the other hand, lower plasma VEGF levels were reported in patients with FM in comparison to controls (Blanco et al., 2010). These scarce and contradictory results on VEGF levels in FM reflects the necessity to carry out further researches in order to clarify the involvement of this molecule in

this complex syndrome. Interestingly, our results have also revealed significant associations between serum VEGF levels and the maximum, minimum, and mean temperatures of the thenar eminence and with the maximum temperature of the hypothenar eminence at the palmar site of the non-dominant hand in patients with FM, not finding significant associations in healthy women. These results suggest that VEGF could be related to dysregulation of hands temperature in patients with FM, probably by contributing to alter peripheral vascular blood flow in these patients. In this line, it has been suggested that altered serum VEGF levels could be associated with blood microcirculation abnormalities and endothelial capillarity disorders in patients with FM (Blanco et al., 2010).

CGRP is another vasoactive compound, located in the C and Aδ peptidergic fibers, with important functions in microcirculation and blood flow regulation due to its vasodilatory capacity (Russell et al., 2014). Our results did not show statistically significant differences in serum CGRP levels between women with FM and healthy women ($p = 0.078$). The only available study that measured CGRP in FM showed that patients had significantly higher serum levels than controls (Korucu et al., 2020). In the present study, we failed to find significant interactions between serum CGRP levels and the peripheral and central temperatures measured in our study participants, suggesting that CGRP does not seem to be related to the dysregulation of hands temperature of FM patients. To our knowledge, this is the first study that assess the associations between CGRP and the peripheral blood microcirculation and thermogenesis in patients with FM. Therefore, future studies are required to verify the present results.

Regarding the limitations of the study, we should mention the following: (i) the small sample size, thus additional studies with larger sample size are required to confirm our results; (ii) this is a cross-sectional study, therefore no causal conclusions can be obtained; (iii) an intra-subject variability could exist in the thermographic record (Clark et al., 1999) that we have tried to minimize following the recommendations of the European Association of Thermogoly; (iv) we have not recorded the menstrual cycle of the women, which could disturb the reflex vascular response (Lafferty et al., 1985); (v) the exclusion of participants with neurological disorders was carried out through a questionnaire where patients indicated if they presented upper limb neurological disturbs or reported a previous electromyography exam. The possibility of not having detected any neurological pathology in the participants or that these pathologies had not been previously diagnosed could affect the interpretation of the present results; and (vi) we enrolled only women due to the higher prevalence of this chronic condition in women than in men (Collado et al., 2014; Mas et al., 2008). Despite of these limitations, the present study is the first one that analyze the associations among serum VEGF and CGRP levels with peripheral temperature of the skin of the hands, as expression of the vascular response, and with the core body temperature in women diagnosed with FM and in healthy women.

As the clinical implications of the results of the present manuscript, the thermographic images of the peripheral temperature are an easy and sensitivity tool to reflect the peripheral vascular response. The differences in hands temperature between FM patients and controls could be used to facilitate the diagnosis of this complex syndrome. Additionally, the relationships found between the peripheral temperature of hand skin and serum VEGF levels only in patients with FM would help distinguish between patients and healthy subjects.

5. Conclusions

In the light of the results, mild associations were observed between serum VEGF levels and the peripheral temperature of the skin in hand areas in patients with FM in comparison to healthy controls. Therefore, our results failed to show a clear relationship between this vasoactive molecule and vasodilation of the hands in women with FM. Further studies are needed in order to clarify the role of VEGF on the neurovascular response in FM.

CRediT authorship contribution statement

Antonio Casas-Barragán: Investigation; Conceptualization; Writing - Review & Editing. **María Carmen García-Ríos**: Investigation; Methodology. **Alma Rus**: Resources; Writing - Original Draft. **Rosa María Tapia-Haro**: Resources; Data Curation. **María Correa-Rodríguez**: Formal analysis; Data Curation; Writing - Original Draft. **María Encarnación Aguilar-Ferrándiz**: Formal analysis; Methodology; Writing - Review & Editing.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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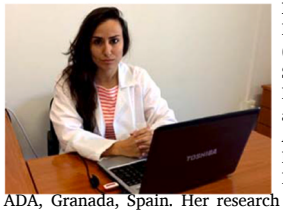

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