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Association of autonomic dysfunction with disease severity in individuals with primary fibromyalgia syndrome: A cross-sectional study

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Abstract

Fibromyalgia syndrome is a musculoskeletal condition and presents with fatigue, sleep disturbances, cognitive symptoms, and heightened sensitivity to touch. Autonomic dysfunction is an associated symptom observed in fibromyalgia. The present study examines the association between autonomic dysfunction and fibromyalgia severity. The study enrolled 144 individuals based on the American College of Rheumatology diagnostic criteria (2010) for fibromyalgia. Autonomic functions were assessed using heart rate variability and Ewing's battery of tests. Fibromyalgia Impact Questionnaire-Revised was used to explore fibromyalgiya severity. A varying degree of fibromyalgia severity was observed in the enrolled individuals with associated increases in pain sensitivity and intensity. Autonomic dysfunction was present in 45.8% (66) of individuals and 8.3% (12) individuals had definite autonomic dysfunction. No correlation was found between fibromyalgia severity and level of autonomic dysfunction. Additionally, no difference was observed in the levels of pain or daily functioning among the three categories of cardiac autonomic dysfunction. Different levels of autonomic dysfunction may be associated with varying levels of fibromyalgia severity, but no definite grade of autonomic dysfunction is associated with a particular grade of severity of fibromyalgia.

Conclusion: Autonomic interaction with chronic pain requires further exploration, considering potential confounders that may impact both factors.

Keywords: Autonomic dysfunction in fibromyalgia, fibromyalgia severity and autonomic dysfunction, fibromyalgia severity, chronic pain and autonomic dysfunction, heart rate variability in primary fibromyalgia

INTRODUCTION

Fibromyalgia syndrome (FMS), a chronic musculoskeletal condition, is characterized by abnormally increased sensitivity to touch, fatigue, sleep disturbances, and/or cognitive symptoms.[1,2] Though the exact pathophysiology of FMS remains unclear, several factors, including genetic, environmental, psychosocial variables, and sleep disturbances, have been suggested as the predisposing factors for its development.[3-6] Additionally, alteration in central pain pathways, leading to hyperalgesia or central sensitization (CS), and exaggerated sympathetic response responsible for generating as well as sustaining chronic pain in FMS are also the suggested models for its development.[4,7] Though chronic pain is the primary complaint of fibromyalgia, associated symptoms like dizziness, palpitation on standing, syncope, and orthostatic hypotension suggest autonomic dysfunction (AD) among these patients of FMS, which impacts their quality of life.[1,8]

Autonomic alteration may impact pain perception as nociceptive and autonomic nerve fibers work together and may impact each other.[9-11] Sympathetic hyperactivity may trigger regional ischemia and small fibre neuropathy leading to pain, being further modified by genetic and environmental factors like stress, anxiety, dry mouth/eye, irritable bowel or trauma, and/or infection (herpes, HIV, Hepatitis C).[10,12] Continuous sympathetic hyperactivity can cause the sprouting of dorsal root ganglia, which has been suggested to cause symptoms of peripheral sensitization like pain, allodynia, and/or

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paraesthesia, etc.[9-13] Autonomic dysfunction has been suggested to either be a cause or effect of fibromyalgia, secondary to central sensitization.[9,14] The inconsistencies in ANS among individuals with FMS have been suggested to be due to the presence of diverse subgroups among FMS.[9,15,16]

Several studies have shown an association of AD in FMS and few others have suggested clinical subgroups of FMS individuals but none have explored the association of AD with FMS severity.[17–19] Understanding the intricate relationship of AD and FMS may pave the way for improved diagnostic, therapeutic or rehabilitative approaches. The present study elucidates the association of AD with FMS severity in a large population from central India.

METHODS

Study design and ethics

It was a cross-sectional study conducted to explore the relationship of AD with the severity of FMS. The study was done in accordance with the Declaration of Helsinki's ethical principles and was conducted after approval from the institute's ethics committee. All the patients provided written informed consent for participation in this study.

Participants

All patients of primary fibromyalgia were screened with the American College of Rheumatology(ACR) 2010 diagnostic criteria for FMS, which is the official FMS diagnostic criteria with a sensitivity of 96.6% and a specificity of 91.8% for discriminating FMS from rheumatic arthritis and osteoarthritis.[1] A person is considered to have FMS if widespread pain index(WPI) score≥7 and symptom score (SS)≥5 or WPI score is 3–6 and SS score≥9, symptoms remain at same level for 3 months and no other disorder otherwise explain the pain.[1] 150 patients attending neurology OPD who satisfied all three criteria of ACR 2010 for fibromyalgia were invited to participate in this study. Finally, 144 patients of age > 18 years were enrolled. Patients who denied consent, pregnant females and individuals with conditions like hypertension, diabetes, hypothyroidism, any inflammatory or autoimmune diseases, or other chronic neurological conditions were excluded.

Study procedure

Demographic characteristics, including age, gender, weight, and height of the participants, were recorded, and body mass index (BMI) was calculated. All the individuals were assessed for severity of pain and status of autonomic functions by Heart rate variability and Ewing's battery of tests.[20] The severity of FMS was graded according to Fibromyalgia Impact Questionnaire-Revised (FIQR).[21]

Pain

Global pain scale (GPS) and Visual analogue scale (VAS) were used to measure pain among FMS individuals.[22,23] GPS was used to assess the multidimensionality of pain. It contains four subscales: activities, feelings, clinical outcome, and individual pain. It is a 20-item, 11-point Likert scale with 0-10 range, indicating strongly disagree to strongly agree.[22] The VAS scale uses points along a line labelled with numbers ranging from 0 to 10, allowing for the measurement of the intensity of pain.[23]

Fibromyalgia Impact Questionnaire-Revised (FIQR)

FIQR is used to assess the severity of FMS. It consists of 21 questions on an 11-point Likert scale ranging from 0-10 and has three domains-function, overall impact, and symptoms scale with a score range of 0-100. Higher scores indicate worsening of symptoms.[21] Grading of the severity of fibromyalgia based on FIQR scores is remission ≤30 (Grade-1); mild severity >30 – 45(Grade-2); moderate severity >46 – 65 (Grade-3); and high severity >65 (Grade-4) was used to categorize FMS severity.[24]

Autonomic function Tests

Heart Rate Variability (HRV) measurement: HRV was recorded during the resting state for 5 minutes by power lab (AD instruments Pt Ltd, Castle Hill Australia). Spectral strength of ECG at 1000 Hz was analysed using fast Fourier transformation (FFT). Standard HRV measures included time domain measures, frequency domain measures and non-linear measures of HRV. Normalized units of low-frequency component (LFnu, 0.04–0.15 Hz), high-frequency component (HFnu, 0.15–0.4 Hz), LFnu:HFnu ratio and total power (Total HRV) were obtained for frequency domain analysis. HF nu is an indicator of status of parasympathetic nervous system(PNS) while LFnu is comprised of sympathetic as well as parasympathetic tone. Thus, LF/HF ratio at a given time indicates the status of sympathetic and parasympathetic nervous system. Indexes calculated on the time domain included standard deviations of the

normal mean NN interval (SDNN), root-mean-square of difference of successive RR intervals (RMSSD) and Average RR interval value, all of which evaluate parasympathetic tone and the percentage of two successive RR intervals that differ by more than 50 milliseconds (pNN50) represents the variation in heartbeat.[25] The non-linear measures included SD1-standard deviation of instantaneous beat-to-beat interval variability, denoting PNS influence, and SD2- the continuous long-term R/R interval variability indicating the sympathetic nervous system.

Ewing's battery of tests: This battery of tests was used to assess the sympathetic and parasympathetic divisions of the Autonomic Nervous System (ANS) during different states of autonomic reactivity. Evaluation of sympathetic division included blood pressure response to 1) Sustained Hand grip; and 2) Head-up tilt at 60° position on tilt-table. On the other hand, the parasympathetic division included assessment of heart rate response to: 1) Head-up tilt at 60° position on tilt-table (30:15 ratio), 2) Valsalva maneuver (Valsalva ratio) and 3) controlled deep breathing with 5 seconds of inhalation and 5 seconds of exhalation (E:I ratio). [20,26,27] Further, individuals were classified into three groups as (1) No CAN (cardiac autonomic neuropathy), (2) Early CAN, and (3) Definite CAN based on the results of Ewing's battery of tests. Individulas with all Ewing's tests normal- No CAN; those with 1 abnormal heart rate test or two borderline tests – Early CAN; and Individuals with 2 abnormal tests and/or presence of orthostatic hypotension as- Definite CAN.[20,28]

Statistical analysis

Microsoft Excel was used to input, screen, and record the data. Statistical package for social sciences (SPSS) version 16 was used to analyse the data. Tests of normality was done using Shapiro-wilk test. Mean and standard deviation was used for parametric data, while median (interquartile range) was used for non-parametric data. Unpaired T test or Mann-Whitney U Test was done for intergroup comparisons. Cronbach's alpha was used to calculate Internal consistency. A value of $p<0.05$ was considered statistically significant for all tests.

RESULTS

One hundred and forty-four individuals diagnosed with primary fibromyalgia syndrome were enrolled in the study. Participants were relatively young with a mean age of 40.31±11.16years. More than 90%(132) were females, with a mean BMI of 25.53±4.59 and mean ACR score of 17.67±3.89. All the individuals of FMS were categorized into 4 grades according to FIQR scoring i.e remission (N=14), mild (N=47), moderate(N=65), and severe (N=18) respectively. The internal consistency (Cronbach's alpha) of WPI was 0.722, of SS was 0.720 and of total ACR 2010 was 0.729 in our patient group. (Table 1).

The pain scores on all the scales showed increment as per the severity grading of FMS, and the scores were significantly higher for FIQR Grade 3 as well as Grade 4 compared to grade 1 and 2 (p=0.0001). (Table 2) There was no association between FMS severity and BMI of the individuals (p=0.798). (Table 2)

Further, No differences were observed either on ewings battery of tests or on the HRV parameters of the patients with different grading of FMS severity. (Figure 1,2) Values of 30:15 ratio increased with increasing grade of FIQR, though no specific trend could be seen with E:I ratio and Valsalva ratio. (Figure 1) The systolic and diastolic blood pressure were within normal range and pulse rate was also within normal range

Table 1: Baseline characters of the participants

Variables		Mean ± SD (N=144)
Age in year		40.31±11.16
Weight in kg		63.72±10.81
Height in ft		5.19±0.36
BMI		25.53±4.59
Gender	Female	91.7%(132)
	Male	8.3%(12)
WPI		10.69±3.11
SSS		5.22±1.41
Total ACR		17.67±3.89
FIQR		48.78±13.31
VAS		6.81±1.55
GPS		51.67±13.96
SBP		120.38±12.10
DBP		77.09±8.29
Pulse		73.43±10.20

Data presented as N(%) and mean± SD; SBP- systolic blood pressure; DBP- diastolic blood pressure; BMI- Body mass index; VAS- Visual analogue scale for pain; GPS- Global pain scale; FIQR- Revised fibromyalgia impact questionnaire; WPI- Widespread pain index; SSS- Symptom severity Score; ACR- American college of rheumatology diagnostic 2010 score.

Table 2: Comparison of pain severity as per severity grading of FMS

Variable	FIQRGrade1 (N=14)	FIQRGrade2 (N=47)	FIQR Grade3 (N=65)	FIQR Grade4 (N=18)	F	P
BMI	25.84±4.03	25.98±4.80	25.33±4.78	24.86±3.84	0.338	.798
WPI	8.21±1.12^{cd}	9.70±2.39^{cd}	11.50±3.26^{ab}	12.27±3.47^{ab}	8.795	.0001
SSS	4.07±1.32^{cd}	4.87±1.31^{cd}	5.53±1.40^{ab}	5.88±1.07^{ab}	7.297	.0001
Total ACR	13.85±1.91^{cd}	16.12±2.77^{cd}	18.95±3.80^{ab}	20.05±4.30^{ab}	14.893	.0001
FIQR	26.63±2.02^{bcd}	39.71±4.26^{acd}	54.70±6.15^{abd}	68.35±11.22^{abc}	170.290	.0001
VAS	5.50±1.22^{cd}	6.61±1.31	7.01±1.66^{a}	7.61±1.33^{a}	6.113	.001
GPS	36.04±10.80^{cd}	43.93±11.68^{cd}	57.21±9.82^{ab}	64.05±13.06^{ab}	30.381	.0001

Data presented as and mean± SD; P<0.05 is significant "*".VAS- Visual analogue scale for pain;GPS- global pain scale; FIQR- Revised fibromyalgia impact questionnaire; BMI- Body mass index; WPI- Widespread pain index; SSS- Symptom severity Score; ACR- American college of rheumatology diagnostic 2010 score. "a" significant difference with FIQRGrade1; "b" significant difference with FIQRGrade2; "c" significant difference with FIQRGrade3; "d" significant difference with FIQRGrade4.

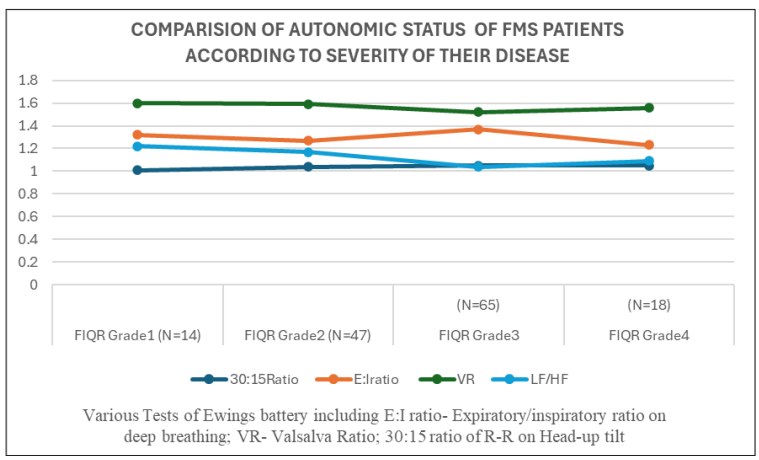

Figure 1. Comparison of Autonomic status of FMS patients according to severity of their disease

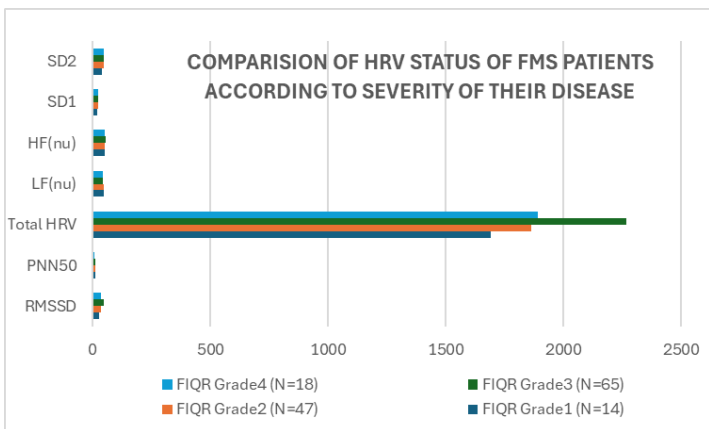

Figure 2. Comparison of HRV status of FMS patients according to severity of their disease
Data presented as mean± SD; Total HRV- Total power of Heart rate variability; RMSSD, root-mean square of the difference of successive RR intervals;pNN50-frequency of two consecutive RR intervals differing by more than 50 ms; LF(nu)- Low Frequency normalised unit; HF(nu), High frequency normalised unit;. LF/HF, LF/HFratio;.SD1- standard deviation of short term RR variability; SD2- standard deviation of long-term RR variability; P<0.05 is significant "*",

Table 3: Autonomic Function dysfunction as per Fibromyalgia syndrome severity

FMS Severity	AFT Normal (No CAN)	Early Dysfunction (early CAN)	Definite Dysfunction (Definite CAN)
FIQR grade 1 (N=14)	5 (35.7%)	8(57.1%)	1 (7.1%)
FIQR grade 2 (N=47)	27 (57.4%)	15 (31.9%)	5 (10.6%)
FIQR grade 3 (N=65)	38 (58.5%)	21 (32.3%)	6 (9.2%)
FIQR grade 4 (N=18)	8 (44.4%)	10 (55.6%)	0

Data presented as N(%); FIQR- Revised fibromyalgia impact questionnaire.

across all the groups of severity of fibromyalgia. The Total HRV was lowest for Grade 1 FIQR group and highest for Grade 3 FIQR group. However, no significant differences were observed among any of the groups based on severity of FMS. (Figure 2)

FIQR and ANS

All the participants were classified based on their AD grading in three categories as having no CAN, early CAN, and definite CAN. 66(45.8%) patients had AD, out of which 54(37.5%) had early CAN and 12(8.3%) had definite CAN (Table 3).

No differences were observed in pain level WPI (p= 0.617), SSS (p= 0.794), VAS (p= 0.423), GPS (p= 0.460), the activity of daily routines FIQR (p= 0.564) as well as total ACR score (p= 0.882) of all the three categories with and without AD (Table 4).

DISCUSSION

Present study was conducted to assess the status of autonomic functions in individuals with fibromyalgia and to explore its association with FMS severity. There was an increase in pain sensitivity as well as in other associated symptoms with the disease severity as assessed on FIQR. The internal consistency of FIQR was comparable to that reported by Galvez-Sánchez *et al*.[29] AD was present in 66(45.8%) patients, of which only 12(8.3%) patients had definite CAN. No association was observed between the severity of FMS and the level of AD in this study, however, there is conflicting literature on this subject with some suggesting that AD plays an important role in the etiopathogenesis of FMS while others could not find this association.[30,31]

Several studies have suggested that fibromyalgia is exclusively characterized by sympathetic dominance, while few others have demonstrated a reduction in both sympathetic and parasympathetic activity in FMS patients.[10,32,33,34] Participants in the present study demonstrated a wide spectrum of autonomic derangements. Despite the substantial sample size, the values observed were within the normative range. This aligns with findings from comparable studies where the disease group exhibited heightened sympathetic activity when compared to the control group, but these values were within the normative boundaries (Table 5).[15,31,35] Singh *et al*. in their cross-sectional study reported no association of AD in patients with mild to moderate grade FMS.[31] Though Kulshreshtha *et al*. reported higher sympathetic activity among FMS patients compared to controls, however,

Table 4: Status of Pain and FIQR Staging as per the gradation of autonomic function dysfunction

VARIABLEs	No CAN (N=78)	Early CAN (N=54)	Definite CAN (N=12)	F	P Value
WPI	10.46±2.97	11.00±3.44	10.83±2.55	0.485	0.617
SSS	5.29±1.39	5.14±1.49	5.08±1.24	0.232	0.794
Total ACR	17.52±3.74	17.87±4.23	17.75±3.49	0.126	0.882
FIQR	49.46±12.96	48.64±14.36	45.04±10.72	0.576	0.564
VAS	6.84±1.51	6.88±1.63	6.25±1.48	0.867	0.423
GPS	52.92±14.10	50.55±14.16	48.58±12.04	0.780	0.460

Data presented as and mean± SD; P<0.05 is significant "*".VAS- Visual analogue scale for pain;GPS- global pain scale; FIQR- Revised fibromyalgia impact questionnaire; WPI- Widespread pain index; SSS- Symptom severity Score; ACR- American college of rheumatology diagnostic 2010 score.

Table 5: Comparison of Autonomic status among patients of Fibromyalgia among different studies

Variable	UNIT	Task Force 1996[25]	Kulshrestra *et al*[35] 2012	Singh *et al*[31] 2021	Lee *et al*[17] 2016	Present study
Sample Size			Cases=42 Control=42	Cases=30 Control=30	Cases=35 Control=25	FMS patients = 144
SDNN	Ms	141±39	24.2397 (7.75–83.15)	33.62±12.02	31.5(26.1, 37.2)	42.46±61.80
RMSSD	Ms	27±12	19.7940 (2.51–106.01)	26.41±14.7	26.3(18.1, 36.4)	40.13± 52.83
LF	Ms^2	1170±416			112.8(62.7, 301.7)	
HF	Ms^2	975±203			157.8(67.9, 255.9)	
LF	Nu	54±4	45.8060 (7.3–86.58)	58.58+16.76		44.80±18.98
HF	Nu	29±3	44.2180 (5.54–84.72)	40±15.97		53.27±17.87
LF/HF ratio		1.5-2.0	0.9789 (0.09–14.99)	2.09±1.98	0.9(0.6, 1.4)	1.11±0.93
30:15 ratio	>1.04				1.15(1.07, 1.23)	1.04± 0.07
E:I ratio	>1.21				1.23(1.13, 1.31)	1.31± 0.52
VR	>1.21				1.1((1.07, 1.119)	1.56± 0.26

mean values of LF/HF ratio was less than 1 and LF was within normal limits as suggested by the task force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology.[25,35] (Table 5).

Gockel *et al*. reported sympathetic predominance in patients with higher subjective disability but no association was seen between HRV and pain severity.[36] They further suggested that it is not the severity of perceived pain that alters ANS function, but it is the mental and physical reaction of the patient to pain that may be a crucial link for AD in chronic pain conditions.[36] A recent study has reported a trend of decreasing amplitude and increasing latency in sympathetic skin response (SSR) with increasing neuropathic pain severity in patients with FMS, which contradicts the hypothesis that FMS is a sympathetically maintained neuropathic pain syndrome.[37] Though this finding was not statistically significant, it may be the reason for conflicting results of the pattern of AD among patients with FMS.[37]

Parasympathetic overactivity as was observed in our study (HF>normal) was consistent with the findings of Hazra *et al*. who reported high HF(nu) in FM group compared to control subjects.[9] These values of HF(nu) are comparable to those mentioned by Kulshreshtha *et al*. and Singh *et al*. , and may be due to the physiological and environmental interaction of the autonomic system.[31,35] Periaqueductal gray matter (PAG) in the brainstem plays a crucial role in interaction of pain and autonomic signals. Nociceptive and autonomic signals proceed to cortical regions of the brain to be processed as pain or to modulate descending pathways.[38,39] Thus, it is not only nociception that may alter the integration of pain pathways; some other cofounders, like autonomic signals, also play a crucial role in the severity of chronic pain.

Acute and chronic pain both act as strong stressors, causing maladaptive changes in various systems of the body including ANS. Acute pain leads to increased sympathetic reactivity thus sympathetic hyperstimulation may be predominant in response to nociception. While in chronic pain with prolonged stress, the dynamic flexibility of ANS is reduced which alters the overall adaptation in both internal and external demand.[10,36,40] Thus in chronic pain AD develops with time but the adaptability of a patient for chronicity of pain may create a new threshold level of sympathetic and parasympathetic.[40,41] The differential presentation of FMS clinical clusters might be the reason that no association of AD could be observed with the increasing FMS severity criteria used in the present study. FMS severity may stem from CNS sensitization, inflammation, and/or vascular dysfunction, and not just SNS abnormalities. Central sensitization leads to amplified pain perception through increased synaptic excitability

and neuroinflammation, independent of SNS influence.[42,43] Microvascular dysfunction results in impaired capillary blood flow and regional ischemia, contributing to widespread muscle pain and fatigue.[44,45] Additionally, endothelial dysfunction, characterized by arterial stiffness and impaired vasodilation, further dysregulates blood flow, exacerbating pain perception.[46] These findings suggest that FMS severity is driven by CNS hypersensitivity, inflammation, and vascular dysfunction rather than SNS abnormalities alone, highlighting the need for broader research perspectives. Though this study included a large number of FMS individuals, however, due to its cross-sectional study design, it had limited ability to establish causality between autonomic dysfunction (AD) and fibromyalgia syndrome (FMS) severity. Future longitudinal studies could be done for better understanding the temporal relationship between AD and FMS severity. The study population was limited to individuals from central India, which may impact the generalizability of the findings to other populations. Cultural, genetic, and environmental factors can influence the manifestation and severity of FMS and AD.

In conclusion, different levels of Autonomic derangements were observed to be associated with different levels of FMS severity; however, no trend of association could be identified among the individuals with different grades of FMS severity. The body's response to pain differs from person to person, physiologically as well as psychologically; thus, further exploration is required to study the intricate relationship between chronic pain and AD, unraveling the complex neural mechanism.

DISCLOSURE

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Declarations of interest: None

REFERENCES

1. Wolfe F, Clauw DJ, Fitzcharles MA, *et al*. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care Res* (Hoboken). 2010;62(5):600-10. doi:10.1002/acr.20140.
2. Wolfe F, Häuser W. Fibromyalgia diagnosis and diagnostic criteria. *Ann Med* 2011;43(7):495-502. doi:10.3109/07853890.2011.595734.
3. Banfi G, Diani M, Pigatto PD, Reali E. T cell subpopulations in the physiopathology of fibromyalgia: Evidence and perspectives. *Int J Mol Sci* 2020;21(4):1186. doi:10.3390/ijms21041186.
4. Staud R, Vierck CJ, Cannon RL, Mauderli AP, Price DD. Abnormal sensitization and temporal summation of second pain (wind-up) in patients with fibromyalgia syndrome. *Pain* 2001;91(1-2):165-75. doi:10.1016/s0304-3959(00)00432-2.
5. Mease P. Fibromyalgia syndrome: review of clinical presentation, pathogenesis, outcome measures, and treatment. *J Rheumatol Suppl* 2005;75:6-21.
6. Tomašević TS, Pjević M, Bošković K. Fibromyalgia: Up to date aspects of patophysiology, diagnosis and treatment. *Med Pregl* 2010;63(7-8):507-11. doi:10.2298/mpns1008507t.
7. Mathias CJ, Bannister SR (eds): Autonomic failure. A textbook of clinical disorders of the autonomic nervous system, 5edn. New York: Oxford University Press, 2013.10.1093/med/9780198566342.001.0001
8. Bou-Holaigah I, Calkins H, Flynn JA, *et al*. Provocation of hypotension and pain during upright tilt table testing in adults with fibromyalgia. *Clin Exp Rheumatol* 1997;15(3):239-46.
9. Hazra S, Venkataraman S, Handa G, *et al*. A cross-sectional study on central sensitization and autonomic changes in fibromyalgia. *Front Neurosci* 2020;14:788. doi:10.3389/fnins.2020.00788.
10. Martinez-Lavin M. Biology and therapy of fibromyalgia. Stress, the stress response system, and fibromyalgia. *Arthritis Res Ther* 2007;9(4):216. doi:10.1186/ar2146.
11. Garcia-Hernandez A, de la Coba P, Reyes Del Paso GA. Central sensitisation pain and autonomic deficiencies in fibromyalgia. *Clin Exp Rheumatol* 2022;40(6):1202-9. doi:10.55563/clinexprheumatol/n280oi .
12. Buskila D, Atzeni F, Sarzi-Puttini P. Etiology of fibromyalgia: the possible role of infection and vaccination. *Autoimmun Rev* 2008;8(1):41-3. doi:10.1016/j.autrev.2008.07.023
13. Di Franco M, Iannuccelli C, Alessandri C, *et al*. Autonomic dysfunction and neuropeptide Y in fibromyalgia. *Clin Exp Rheumatol* 2009;27(5 Suppl 56):S75-S78..
14. Jay GW, Barkin RL. Fibromyalgia. *Dis Mon* 2015;61(3):66-111. doi:10.1016/j.disamonth.2015.01.002.
15. Plazier M, Ost J, Stassijns G, De Ridder D, Vanneste S. Pain characteristics in fibromyalgia: understanding the multiple dimensions of pain. *Clin Rheumatol* 2015;34(4):775-83. doi:10.1007/s10067-014-2736-6.
16. Giesecke T, Williams DA, Harris RE, *et al*. Subgrouping of fibromyalgia patients on the basis of pressure-pain thresholds and psychological factors. *Arthritis Rheum* 2003;48(10):2916-22. doi:10.1002/art.11272.
17. Lee KE, Choi SE, Kang JH, *et al*. Comparison of heart rate variability and classic autonomic testing for detection of cardiac autonomic dysfunction in patients with fibromyalgia. *Int J Rheum Dis* 2018;21(4):804-12. doi:10.1111/1756-185X.12858.
18. Kulshreshtha P, Deepak KK, Yadav RK, Mukherjee D. Cardiac autonomic neuropathy in fibromyalgia: Revisited. *J Back Musculoskelet Rehabil* 2022;35(1):111-7. doi:10.3233/BMR-200209.

19. Kang JH, Kim JK, Hong SH, Lee CH, Choi BY. Heart rate variability for quantification of autonomic dysfunction in fibromyalgia. *Ann Rehabil Med* 2016;40(2):301-9. doi:10.5535/arm.2016.40.2.301.
20. Ewing DJ, Martyn CN, Young RJ, Clarke BF. The value of cardiovascular autonomic function tests: 10 years experience in diabetes. *Diabetes Care* 1985;8(5):491-8. doi:10.2337/diacare.8.5.491.
21. Bennett RM, Friend R, Jones KD, Ward R, Han BK, Ross RL. The Revised Fibromyalgia Impact Questionnaire (FIQR): validation and psychometric properties. *Arthritis Res Ther* 2009;11(4):R120. doi:10.1186/ar2783.
22. Wan TTH, Gurupur V, Patel A. A longitudinal analysis of total pain scores for a panel of patients treated by pain clinics. *Health Serv Res Manag Epidemiol* 2019;6:2333392818788420. doi:10.1177/2333392818788420.
23. Plazier M, Ost J, Stassijns G, De Ridder D, Vanneste S. Pain characteristics in fibromyalgia: understanding the multiple dimensions of pain. *Clin Rheumatol* 2015;34(4):775-83. doi:10.1007/s10067-014-2736-6.
24. Salaffi F, Di Carlo M, Arcà S, Galeazzi M. Categorisation of disease severity states in fibromyalgia: a first step to support decision-making in health care policy. *Clin Exp Rheumatol* 2018;36(6):1074-81.
25. Malik M. Heart rate variability: standards of measurement, physiological interpretation and clinical use:Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Circulation* 1996;93(5):1043-65. 10.1111/j.1542-474X.1996.tb00275.x
26. Wirch JL, Wolfe LA, Weissgerber TL, Davies GA. Cold pressor test protocol to evaluate cardiac autonomic function. *Appl Physiol Nutr Metab* 2006;31(3):235-43. doi:10.1139/h05-018.
27. Sharma RK, Deepak KK, Bijlani RL, Rao PS. Short-term physical training alters cardiovascular autonomic response amplitude and latencies. *Indian J Physiol Pharmacol* 2004;48(2):165-73.
28. Spallone V, Bellavere F, Scionti L, *et al*. Recommendations for the use of cardiovascular tests in diagnosing diabetic autonomic neuropathy. *Nutr Metab Cardiovasc Dis* 2011;21(1):69-78. doi:10.1016/j.numecd.2010.07.005.
29. Galvez-Sánchez CM, de la Coba P, Duschek S, Reyes Del Paso GA. Reliability, factor structure and predictive validity of the widespread pain index and symptom severity scales of the 2010 American College of Rheumatology Criteria of Fibromyalgia. *J Clin Med* 2020;9(8):2460. doi:10.3390/jcm9082460.
30. Martinez-Lavin M. The autonomic nervous system and fibromyalgia. *J Musculoskelet Pain* 2002; 10: 221-8. https://doi.org/10.1300/J094v10n01_18
31. Singh R, Rai NK, Rastogi A, Endukuru C, Joshi A, Mishra SS. Impact of sleep disturbances and autonomic dysfunction on the quality of life of patients with fibromyalgia. *J Basic Clin Physiol Pharmacol* 2021;32(6):1021-9. doi:10.1515/jbcpp-2020-0007.
32. Martínez-Lavín M, Hermosillo AG, Rosas M, Soto ME. Circadian studies of autonomic nervous balance in patients with fibromyalgia: a heart rate variability analysis. *Arthritis Rheum* 1998;41(11):1966-71. doi:10.1002/1529-0131(199811)41.11<1966::AID-ART11>3.0.CO;2-O.
33. Pickering G, Achard A, Corriger A, *et al*. Electrochemical skin conductance and quantitative sensory testing on fibromyalgia. *Pain Pract* 2020;20(4):348-56. doi:10.1111/papr.12857.
34. Reyes Del Paso GA, de la Coba P. Reduced activity, reactivity and functionality of the sympathetic nervous system in fibromyalgia: An electrodermal study. *PLoS One* 2020;15(10):e0241154. doi:10.1371/journal.pone.0241154.
35. Kulshreshtha P, Gupta R, Yadav RK, Bijlani RL, Deepak KK. A comprehensive study of autonomic dysfunction in the fibromyalgia patients. *Clin Auton Res* 2012;22(3):117-22. doi:10.1007/s10286-011-0150-6.
36. Gockel M, Lindholm H, Niemistö L, Hurri H. Perceived disability but not pain is connected with autonomic nervous function among patients with chronic low back pain. *J Rehabil Med* 2008;40(5):355-8. doi:10.2340/16501977-0172.
37. On AY, Tanigor G, Baydar DA. Relationships of autonomic dysfunction with disease severity and neuropathic pain features in fibromyalgia: is it really a sympathetically maintained neuropathic pain? *Korean J Pain* 2022;35(3):327-35. doi:10.3344/kjp.2022.35.3.327.
38. Benarroch EE. The central autonomic network: functional organization, dysfunction, and perspective. *Mayo Clin Proc* 1993;68(10):988-1001. doi:10.1016/s0025-6196(12)62272-1.
39. Cortelli P, Giannini G, Favoni V, Cevoli S, Pierangeli G. Nociception and autonomic nervous system. *Neurol Sci* 2013;34 Suppl 1:S41-S46. doi:10.1007/s10072-013-1391-z.
40. Greening J, Lynn B, Leary R. Sensory and autonomic function in the hands of patients with non-specific arm pain (NSAP) and asymptomatic office workers. *Pain* 2003;104(1-2):275-81. doi:10.1016/s0304-3959(03)00010-1.
41. Kruglov D, McGuckin D. The role of autonomic nervous system in pain chronicity [Internet]. *Physiology IntechOpen* 2023. http://dx.doi.org/10.5772/intechopen.112154.
42. Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. *J Pain* 2009;10(9):895-926. doi:10.1016/j.jpain.2009.06.012.
43. Ji RR, Nackley A, Huh Y, Terrando N, Maixner W. Neuroinflammation and central sensitization in chronic and widespread pain. *Anesthesiology* 2018;129(2):343-66. doi:10.1097/ALN.0000000000002130.
44. Coderre TJ. Contribution of microvascular dysfunction to chronic pain. *Front Pain Res (Lausanne)* 2023;4:1111559. doi:10.3389/fpain.2023.1111559.
45. Esen E, Çetin A. Microvascular functions in patients with fibromyalgia syndrome: effects of physical exercise. *Turk J Phys Med Rehabil* 2017;63(3):215-23. doi:10.5606/tftrd.2017.351.
46. Lee JH, Cho KI, Kim SM, Lee HG, Kim TI. Arterial stiffness in female patients with fibromyalgia and its relationship to chronic emotional and physical stress. *Korean Circ J* 2011;41(10):596-602. doi:10.4070/kcj.2011.41.10.596.