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REVIEW ARTICLE

Coexistence of fibromyalgia syndrome and inflammatory rheumatic diseases, and autonomic cardiovascular system involvement in fibromyalgia syndrome

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Abstract

The spectrum of symptoms represented by fibromyalgia syndrome (FMS) has a profound effect on daily activities and impairs the quality of life. A considerable proportion of patients with inflammatory rheumatic diseases (IRDs) fulfill the FMS criteria, which can complicate the diagnosis, treatment, and follow-ups of IRD. In addition, the coexistence of FMS may cause unnecessary laboratory and radiological assessments. Several mechanisms have been proposed that may have a role in the etiopathogenesis of FMS, one of which is autonomic dysregulation. In studies evaluating cardiac autonomic dysfunction based on heart rate variability (HRV), there has been found to be a decrease in HRV and dominance of the sympathetic nervous system. Autonomic reactivity reflects modulations of several functions to overcome the existing state and conditions. Blunted autonomic reactivity has been found in some FMS patients, which makes it difficult for these patients to respond appropriately to unexpected stress sources that occur during daily living activities. Baroreceptor signals have an inhibitory influence on the central nervous system, and these impulses cause pain suppression. From this perspective, there are studies that have suggested the involvement of diminished baroreflex sensitivity in the etiology of FMS. The risk of endothelial dysfunction and increased arterial stiffness have been shown to occur in FMS patients due to autonomic dysfunction, sympathetic nervous system dominance, chronic stress, and pain. There is also evidence linking FMS with the risk of atrial and ventricular arrhythmias. Considering all these cardiovascular autonomic dysfunctions, tests that can confirm abnormalities should be performed when suspicion arises. There is a need for specific pharmacological and non-pharmacological treatment alternatives to be identified for subgroups of patients with cardiovascular system abnormalities.

Key points

- *The frequency of FMS accompanying inflammatory rheumatic diseases is considerable and this coexistence leads to troubles in evaluating treatment response and determining appropriate medical treatment options in inflammatory rheumatic diseases.*
- *Various cardiovascular autonomic abnormalities have been described in FMS patients. Among these, the most emphasized are autonomic dysfunction, the disruption of the balance between the sympathetic-parasympathetic nervous systems, blunted autonomic reactivity to acute stress, changes in baroreflex sensitivity, increased arterial stiffness, and electrophysiological alterations.*
- *Autonomic cardiovascular dysfunction may be involved in the complex etiopathogenesis of the fibromyalgia syndrome and may trigger at least some symptoms.*

Keywords Autonomic nervous system · Cardiovascular abnormality · Dysautonomia · Fibromyalgia · Rheumatic diseases

Part of the Topical Collection entitled 'Cardiovascular Issues in Rheumatic Diseases'

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Introduction

Fibromyalgia syndrome is a rheumatic disease with chronic widespread pain at its center, and which can be accompanied by sleep disorders, stiffness, tiredness, and various somatic-cognitive signs. In contrast to the wide range of symptoms noted, physical examination findings are limited and far from presenting disease-specific features [1]. FMS influences daily living activities to a degree that cannot be

ignored. The consequence of this symptom complex has devastating impacts on quality of life, labor productivity, and social life [2].

Patients with inflammatory rheumatic diseases (IRDs) often meet the criteria for FMS, which can complicate the diagnosis and treatment of IRDs [3]. The definitive prevalence of this accompanying FMS in IRDs remains a matter of debate [4]. The coexistence of FMS and IRDs, in addition to the influence on the underlying inflammatory disorder, is a prominent topic. Evaluating disease activity in IRDs depends in part on self-reported scales [5, 6]. However, FMS can trigger a variety of symptoms unrelated to the inflammatory conditions, which can disrupt disease activity assessments. This may result in unnecessary laboratory and radiological evaluations, inappropriate dose escalation, or treatment changes.

The autonomic nervous system regulates numerous processes of our body to sustain homeostasis. It requires multiple reflex arcs as a regulation procedure to maintain body homeostasis. These reflex arcs contain an afferent, a central, and an efferent component. An unusual function in the reflex arc, as well as a functional disorder in the autonomic nervous system, can result from a defect, abnormality, or functional error in the afferent, central, or efferent structures of the reflex arc. This condition negatively affects body homeostasis [7].

The etiopathogenesis of FMS has not been fully elucidated. However, it has been suggested that increased sensitivity in the central nervous system and the inadequacy of pain-inhibiting pathways are associated with the process [8, 9]. There is also evidence that autonomic dysregulation may play a role in the emergence of some of the symptoms in FMS [10, 11]. Nevertheless, contradictory results have been reached concerning the model of autonomic nervous system dysfunction. In many studies, elevated sympathetic activity and decreased parasympathetic activity have been detected in FMS [12, 13]. In contrast, other studies have revealed that there is a decrease in autonomic nervous system activity in FMS, in respect of the sympathetic and parasympathetic systems [14, 15]. Alterations in conditions of the cardiovascular system regulate pain processing in the central nervous system and constitute a substantial source of pain relief [16]. Experimentally generated blood pressure increases cause a significant depletion in pain sensibility and tonic blood pressure shows an inverse correlation with the level of pain [17, 18].

In this review, the coexistence of IRDs and FMS and its clinical implications are presented. In an important part of the article, the autonomic cardiovascular system involvement in FMS and its clinical impacts are revealed.

Search strategy

A systematic search strategy was performed on the Web of Science, Scopus, and PubMed/MEDLINE with the following keyword combinations: "Fibromyalgia and Rheumatic Disease" or "Fibromyalgia and Cardiac Disease" or "Fibromyalgia and Cardiovascular Abnormality" or "Fibromyalgia and Heart Disease" or "Fibromyalgia and Heart Disorder" or "Fibromyalgia and Cardiovascular Disease." Mesh terms were used as a basis for keyword determination. Controlled clinical studies, observational studies, reviews, and articles written in English were determined as inclusion criteria. The exclusion criteria were as follows: repeated papers, meeting abstracts, posters, case reports, case series, editorials, commentaries, letters, articles written in languages other than English, and articles not directly related to the subject. This strategy was designed according to the recommendations of Gasparyan et al. [19]. The last update was made on June 18, 2022. The flowchart of the process is presented in Fig. 1.

Assessment of fibromyalgia syndrome coexistence in inflammatory rheumatic diseases

In addition to being primarily diagnosed, FMS can also occur secondary to various underlying disorders [20]. In studies conducted on the general population, the prevalence of FMS has been reported to range from 0.5 to 5%, depending on the diagnosis/classification criteria used [21, 22]. Current literature data have revealed increased prevalence values of FMS in patients with IRD compared to the general population [23–26]. Levy et al. [25] evaluated patients with various IRDs in terms of FMS prevalence. The values for rheumatoid arthritis, systemic lupus erythematosus, spondyloarthritis, polymyalgia rheumatica, and other IRDs were determined as 26%, 28.5%, 7.8%, 6.2%, and 29.1%, respectively. The relatively low prevalence values in the spondyloarthritis and polymyalgia rheumatica group were attributed to male dominance in the spondyloarthritis group and the dramatic positive response to steroid use of the patients in the polymyalgia rheumatica group. Macfarlane et al. [27] used the 2011 American College of Rheumatology criteria (ACR) to assess the coexistence of FMS in patients with axial spondyloarthritis and reported that FMS was detected in 20.7% of 1504 patients with axial spondyloarthritis. There are studies reporting the coexistence of FMS with rates of 48%, 41.9%, and 14.7% for rheumatoid arthritis [28–30]. According to the ACR 1990 and 2016 criteria, primary Sjogren's syndrome FMS co-occurrence was reported to be 18% and 19%, respectively [31]. The higher prevalence of FMS in rheumatic disorders may be triggered by peripheral inflammation. Increased inflammation in peripheral structures causes a growth in the number of inputs that induce FMS pathogenesis. Another aspect that may contribute to FMS is increased central sensitization in patients with IRD [29, 32].

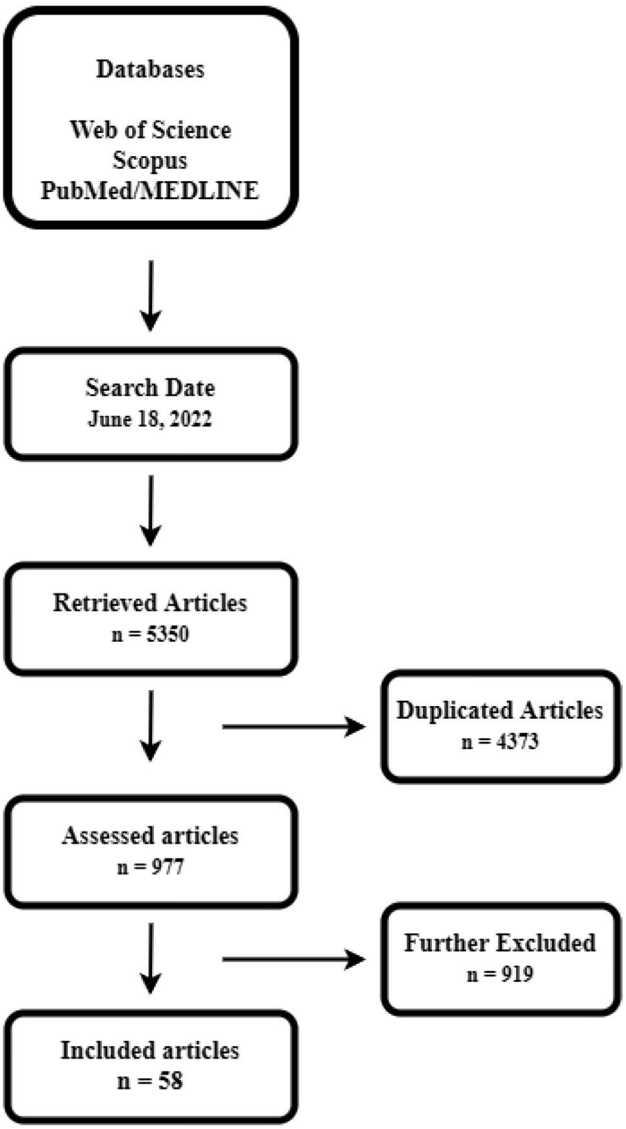

Fig. 1 Flowchart of the review

Widespread body pain is the cornerstone sign of FMS. Fatigue, mental disorders, sleep impairment, psychiatric abnormalities, and stiffness are particular components of this complex clinical picture [1]. This set of symptoms makes it challenging to evaluate disease activity and treatment response in patients with IRD and FMS coexistence [33, 34]. FMS coexistence can result in higher disease activity, particularly in measurements based on self-reported assessments. General health assessment and tender joint count, which are components of the DAS 28 measurement, can be affected by the presence of FMS [28]. Furthermore, FMS existence can result in higher scoring of BASDAI determinants [35]. Therefore, it would be a more accurate approach for clinicians to base disease activity on objective methods, particularly in IRD and FMS co-occurrence. Evaluating acute phase reactants and various biomarkers, as well as confirming synovitis-enthesitis with musculoskeletal ultrasound, will provide a more accurate assessment of disease activity [32, 36, 37].

Cardiovascular autonomic involvement in fibromyalgia syndrome

FMS patients have been reported to have a variety of cardiovascular autonomic anomalies. In this review, the alterations are detailed under the following subtitles:

- Sympathetic and parasympathetic nervous system activity
- Cardiac autonomic reactivity
- Baroreflex sensitivity
- Vascular involvement
- Cardiac electrophysiological changes (Fig. 2)

Sympathetic and parasympathetic nervous system activity

Various techniques have been performed to evaluate the functional activity of the sympathetic nervous system. The most common preferred methods are analysis of heart rate variability (HRV), sympathetic skin response test, tilt table testing, and genetic investigations [38]. A large number of studies have used HRV analysis to determine the cardiac autonomic state of FMS patients. The high-frequency (HF) band of HRV analysis represents parasympathetic cardiac regulation, while the low-frequency (LF) band indicates sympathetic control [39, 40]. In addition, the LF/HF ratio has been suggested as an indicator of sympathovagal balance, which is commonly accepted as mirroring the relative sympathetic contribution to heart rate control [41]. There is also evidence that the HF band reflects parasympathetic activity, while the LF band is affected by both the sympathetic and parasympathetic systems. From this perspective, LF/HF may not represent pure sympathetic activity [42]. Reyes Del Paso et al. [42] compared the HRV, R-R interval, and stroke volume between FMS patients and healthy control subjects. FMS patients displayed lower power in all HRV frequency bands. Significantly lower values were found in the R-R interval and stroke volume in FMS patients. This result was interpreted as the effect of the decrease in the sympathetic and parasympathetic nervous system and reduction in total HRV power in FMS patients. Another article by Reyes Del Paso et al. [43] supported similar findings. Riva et al. [44] evaluated heart rate and catecholamines together in FMS patients and reported reduced sympathetic activity of the adrenal medullary component in the form of lower adrenaline and dopamine levels, and decreased parasympathetic activity in the form of greater resting heart rate. Kulshreshtha

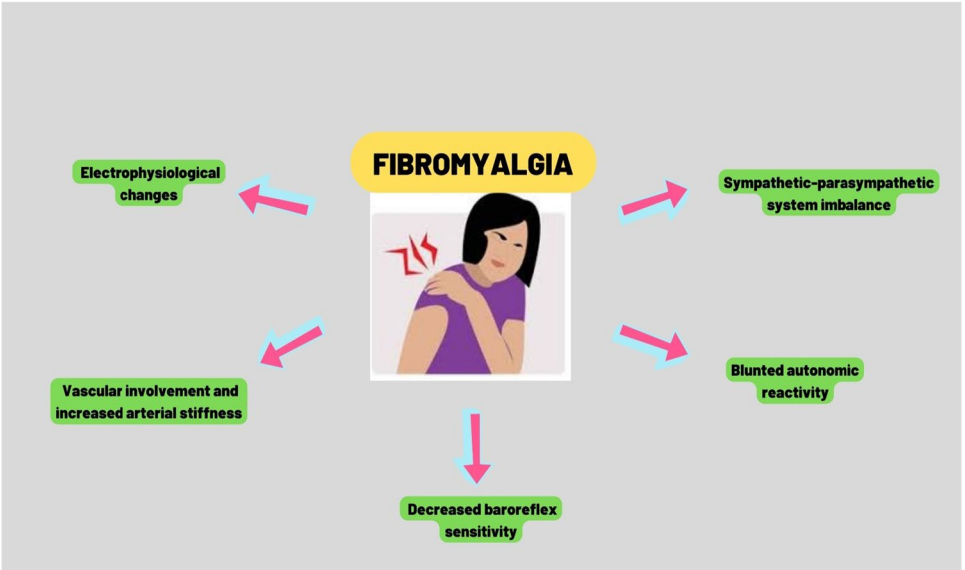

Fig. 2 Cardiovascular autonomic involvement in fibromyalgia syndrome

et al. [45] detected lower levels of HRV parameters in FMS patients. Resting systolic and diastolic blood pressures were higher in FMS patients. In addition, the percentage of HF was found to be decreased as an indicator of attenuated parasympathetic activity. Systolic and diastolic blood pressures were recorded for 24 h and compared between FMS patients and healthy individuals in another study, which revealed that the non-dipper pattern was dominant in FMS patients. This result was attributed to the overactivity of the sympathetic nervous system in FMS [46]. HRV in FMS patients was evaluated during non-REM and REM sleep, and it was reported that parasympathetic activity is weakened during sleep [47]. Lerma et al. [48] showed a decreasing trend in nocturnal HRV parameters with sympathetic nervous system dominance. Zamunér et al. [49] found that FMS patients had an increased LF/HF ratio as well as lower HRV parameters. In another study in which the LF/HF ratio was evaluated in total, during the day, and at night, the values were found to be higher in FMS patients [50]. In contrast, Contreras-Merino did not find a higher resting heart rate and could not confirm sympathetic overactivity in FMS patients [51].

A substantial part of the results supports autonomic dysregulation in FMS patients. Although not all results are compatible with each other, attenuation of the sympathetic and parasympathetic systems occurs together with the decrease in HRV parameters. Moreover, in the resting condition, the sympathetic system becomes dominant.

Cardiac autonomic reactivity

Autonomic reactivity mirrors the regulations of various functions to overcome the current state and conditions. The capacity of organisms to respond to altering environmental situations is indicative of a basic level of adaptation [52]. Individuals with poor autonomic reactivity capacity struggle to adapt to changing conditions and emerging difficulties during daily living activities [53]. Reyes Del Paso et al. [42] evaluated FMS patients during the arithmetic task and reported less pronounced R-R interval alterations compared to healthy individuals. Contreras-Merino et al. [51] assessed the short-term responses during the postural changes in FMS patients and reported lower reactivity status. In a study by da Cunha Ribeiro et al. [54], the cardiac response to graded exercise was examined in FMS patients and there was found to be a lower heart rate response compared to healthy control subjects. In the same study, participants were evaluated during the resting period and it was reported that the compliance of FMS patients with the resting period was also impaired. Blunted cardiac response to experimental pain stimulus in FMS patients has been reported [43]. However, Kulshreshtha et al. [45] did not detect any differences in blood pressures between FMS patients and healthy control subjects in response to the standing test, cold pressor test, and hand grip test. In another study, no difference was found in response to the head-up tilt test [55].

FMS is a heterogeneous disease and the results may vary depending on the predominant symptoms. In addition, sample size, the tests used to evaluate cardiovascular reactivity, age, drug use, and exercise status may affect the results. Based on the data, it is possible that the cardiac response to changing conditions is blunted in a significant proportion of FMS patients. It is apparent that this patient group will struggle with daily living activities and when confronted with unexpected stressors.

Baroreflex sensitivity

The baroreflex system is one of the major components of autonomic cardiovascular control. This system modulates cardiac and vasomotor activity by reflex regulations and plays a regulator role in blood pressure [56]. Signals originating from the arterial baroreceptors reach the nucleus of the tractus solitarius of the central nervous system, which induces vagal neuron activity and limits spinal sympathetic efficiency [57]. In addition to the effect of keeping blood pressure within a certain range, there is also a modulation effect on the central nervous system [58]. Baroreflex sensitivity is negatively correlated with pain intensity in healthy individuals, and this has also been shown in FMS patients [42, 59]. Reyes Del Paso et al. [60] evaluated the cardiac, vasomotor, and myocardial branches of the baroreflex in FMS patients, and decreased baroreflex sensitivity was detected in three sections. In addition, pain level, depression-anxiety scores, sleep disorders, and fatigue were found to be negatively linked to baroreflex sensitivity. Various studies supporting these findings are available in the literature [42, 43, 61]. In contrast, Zamunér et al. [62] did not detect any difference in baroreflex sensitivity between FMS patients and healthy control subjects. This result was attributed to methodological differences and it was reported that no difference could be found in baroreflex sensitivity with traditional methods, but lower baroreflex sensitivity values could be obtained in FMS patients when the method was changed.

Reduced baroreflex sensitivity may contribute to the etiopathogenesis of FMS. This involvement could be linked to increased baroreflex sensitivity, which results in a stronger inhibitory influence on the central nervous system. Furthermore, a putative mechanism is the association between greater baroreflex efficiency and pronounced pain inhibition.

Vascular involvement

In addition to microvascular alterations in FMS, some evidence has been presented that macrovascular disorders may be associated with the particular characteristics of FMS**.** Previous studies have suggested that autonomic dysfunction and sympathetic nervous system dominance may increase the endothelial dysfunction process and cardiovascular disorders in FMS patients [63–65]. Arterial stiffness is an active vascular feature that is affected by the functions and architecture of the larger arteries. It has been demonstrated in various diseases that arterial stiffness is an essential predictor of cardiovascular disorders [66, 67]. This association has also been revealed in IRDs [68–70]. Several studies have shown that arterial stiffness values increase in FMS patients [63, 65, 71, 72]. Advanced arterial stiffness, which is a sign of a decrease in elastin content and an increase in collagen content, can be considered an indicator of the progression of the atherosclerotic process and vessel remodeling [71]. Given that this biomechanical change is associated with cardiovascular disease risk, it would be appropriate to evaluate FMS patients from this perspective, as with IRDs.

Cardiac electrophysiological changes

Several cardiac electrophysiological abnormalities may occur in FMS patients as a result of autonomic dysfunction and altered balance between sympathetic-parasympathetic nervous systems. Early detection of changes in this direction is valuable in terms of preventing cardiovascular morbidity [73]. Aksu et al. [73] examined FMS patients for cardiac electrophysiological abnormalities. The interatrial electromechanical delay values were utilized as a predictor for atrial fibrillation [74]. It was determined that this value was prolonged in FMS patients, which may cause a tendency to atrial fibrillation. In the same study, P and QT dispersions were evaluated and significant increases were found in both parameters. In addition, fragmented QRS was detected more frequently in FMS patients. It has been suggested that heterogeneous depolarization of the ventricular myocardium brought on by ischemia or fibrosis leads to the development of fragmented QRS shape [75]. In another study, FMS patients had a higher rate of supraventricular extrasystoles and supraventricular tachycardia than healthy control subjects. Arrhythmia types and sympathetic activity parameters were found to have significant positive correlations [50]. However, there are also data inconsistent with these results in the literature [76].

Autonomic dysfunction, changes in the sympathetic-parasympathetic nervous system balance, increase in resting blood pressure, and comorbid conditions such as depression-anxiety may cause arrhythmia tendency in FMS patients. However, studies with larger sample sizes and longer follow-ups are needed to support this view, to determine the clinical importance of electrophysiological changes, evaluate their persistence, and reveal the relationships between arrhythmias and cardiovascular complications.

This review has some limitations. The etiopathogenesis of FMS is unclear; therefore, it is challenging to reveal definitive conclusions about the role of cardiovascular alterations in FMS pathogenesis. A direct causality cannot be established between FMS and cardiovascular system abnormalities. The systematic search was performed on the Web of Science, Scopus, and PubMed/MEDLINE. Articles in other databases were not evaluated. In addition, articles other than English were not assessed.

Conclusion

The frequency of FMS accompanying IRDs is considerable, and this coexistence causes difficulties in evaluating treatment response and determining appropriate medical treatment options in IRDs. Various cardiovascular autonomic abnormalities have been described in FMS patients. Among these, the most emphasized are autonomic dysfunction, the disruption of the balance between the sympathetic-parasympathetic nervous systems, and blunted autonomic reactivity to acute stress. It is thought that autonomic cardiovascular dysfunction may play a role in the etiopathogenesis of FMS and may trigger at least some symptoms within the clinical spectrum. Physicians should be more vigilant about possible cardiovascular alterations in patients with FMS. First of all, besides the main clinical signs of FMS, symptoms related to cardiovascular effects should be questioned. It can be appropriate to evaluate patients with suspicion at the first stage with procedures such as tilt test, blood pressure follow-ups spread throughout the day, or electrocardiogram. Particular pharmacological and non-pharmacological treatment options should be determined for subgroups of patients with cardiovascular system dysfunction, and appropriate rehabilitation interventions should be implemented for this patient group.

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Data acquisition and review of the literature: BFK and AA.
Making interpretations: BFK and AA.
Drafting the manuscript: BFK.
Critically reviewing the manuscript: BFK and AA.
Final approval: BFK and AA.

Compliance with ethical standards

Disclosures None.

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