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Impact of sleep disturbances and autonomic dysfunction on the quality of life of patients with fibromyalgia

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Abstract

Objectives: Fibromyalgia, a painful musculoskeletal disorder is associated with sleep disturbances as well as autonomic dysfunction. Pathophysiology of fibromyalgia is yet not clear and neuroanatomical proximity of sleep and autonomic centre prompts probable involvement of the two impacting the quality of life of fibromyalgia patients. Present study was done with the objective to explore the extent of sleep disturbances and/or autonomic dysfunction in fibromyalgia and asses their impact on quality of life of fibromyalgia patients.

Method and materials: Thirty consecutive fibromyalgia patients (diagnosed by ACR 2010) from out-patient department and 30 age-gender matched controls were enrolled after the ethical clearance. All participants were evaluated for: (1) sleep using Pittsburgh sleep quality index and medical outcomes study sleep scale-12 Revised, (2) Quality of life by 36 item short-form health survey-36v2TM and revised fibromyalgia impact questionnaire (only patients). Autonomic functions of patients were evaluated by standard cardiovascular autonomic function tests by Ewing's battery and heart rate variability (5-min) measurement.

Results: Fibromyalgia patients had increased sleep disturbances compared to controls (39.46 ± 11, 59.61 ± 2.31; p=0.0001) and very poor sleep quality (13.63 ± 4.15, 3.03 ± 1.56; p=0.0001) as well as quality of life (p=0.0001) which further deteriorated with increasing severity of fibromyalgia. Twelve patients had autonomic dysfunction but it was neither associated with sleep disturbances nor with quality of life.

Conclusions: Mild to moderate grade fibromyalgia patients have significant sleep disturbance, poor sleep quality which remarkably impacts their quality of life. Autonomic dysfunction is not an early feature of disease. The study suggests that full spectrum of sleep disturbances and sleep quality should be explored in fibromyalgia syndrome (FMS) patients.

Keywords: autonomic dysfunction; fibromyalgia; heart rate variability; quality of life; sleep quality.

Introduction

Fibromyalgia is a disabling condition of chronic and diffuse musculoskeletal pain, tenderness and stiffness. Constellation of other symptoms including fatigue, sleep disturbances, cognitive dysfunction and depression/anxiety make it a complex syndrome addressed as fibromyalgia syndrome (FMS) [1]. Global prevalence of FMS is about 2.7% and it shows female preponderance (3:1) [2]. FMS not only effects the sufferer physically but psychologically as well and thus influences their quality of life (QOL). It poses a major public health problem with a high impact on health care as well as total societal costs. However, studies from India are very limited [3].

Pathophysiology of FMS is still unclear. Factors like neuroendocrine disturbances, autonomic dysfunctions, psychosocial factors, environmental and genetic factors have been implicated to be involved [4, 5]. Sleep disturbances in form of poor sleep induction, frequent awakening and non-restorative sleep have also been found to be associated in more than 90% of FMS patients and is considered as an important part of disease [6]. A reciprocal relationship has been shown to exist between sleep and pain [7]. Autonomic nervous system (ANS) activity is also

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influenced by sleep and shows changes with different stages of sleep [8]. Role of autonomic dysfunction in pathogenesis of FMS is disputed but close neuroanatomical association of centres for both ANS and sleep, prompts probable involvement of sleep dysfunction along with ANS [9]. The multisystem involvement in FMS has also been proposed to be due to ANS dysfunction which has widespread distribution in body [10]. But, studies have reported conflicting results for involvement of ANS in FMS [11]. Some authors have shown normal resting autonomic tone while others reported increased resting sympathetic tone and reduced tone on active stress while few others reported sympathetic hyperactivity with concomitant reduction in parasympathetic activity [10, 12, 13]. Interestingly, association of autonomic dysfunction has also been shown to vary with the severity of FMS [14]. Sleep disturbances and autonomic dysfunctions have a distressing effect on a person's daily activities influencing his professional, social and personal life which ultimately affects the QOL [15, 16].

Though varied involvement of autonomic and sleep disturbances has been shown to be present in FMS patients but their association with severity of FMS and their impact on the QOL of FMS patients is lacking. Due to unavailability of definite treatment of FMS, most of patients suffer from physical and mental pain resulting poor QOL [17]. Knowledge of differential association of sleep and/or autonomic dysfunctions with FMS may help to provide a tailored treatment to these patients. Thus, present study endeavoured to re-explore the association of ANS and sleep disturbances with severity of FMS along with their impact on QOL of these patients.

Materials and methods

Study design

We designed a cross-sectional study to explore the association of sleep and autonomic dysfunction with QOL of patients suffering from FMS. The study was approved by the institutional ethical committee of All India Institute of Medical Sciences Bhopal, India (approval no. IHEC-LOP/2015/STS 0053-2015). It was performed in agreement with the ethical guidelines of the Declaration of Helsinki. All the participants provided written informed consent prior to participation in the study.

Sample selection

Cases: Patients diagnosed with primary fibromyalgia according to American College of Rheumatology criteria (ACR 2010) were enrolled from the out-patient department of neurology. According to ACR 2010 criteria patient is considered to have FMS if symptoms are at same level for 3 months with widespread pain index (WPI) score≥7 and symptom score (SS)≥5 or patients with WPI score 3–6 and SS score≥9 and the patient does not have any other disorder that would otherwise explain the pain [18]. Both genders of ages between 18 and 80 years, who were able to understand and answer simple English, were included in the study. Patients having extenuating circumstances, such as a young child at home, pregnant females; or night-shift work, patients suffering from diabetes, hypertension and other connective tissue disease like systemic lupus erythematosus, endocrine or metabolic disease and neurologic or other neuromuscular diseases were excluded. Thirty-three patients of primary fibromyalgia were recruited for the study but three patients did not turned-up for all the proposed investigations and thus finally only 30 patients were included in the study.

Controls: Age and gender matched 30 apparently healthy individuals, without the complaints of body ache; sleep disturbances, headache, and any other acute illness were included as controls from amongst the attendees of the patients after a written informed consent.

Procedure

We recorded the clinical and socio-demographic data of all participants. They were subjectively evaluated for sleep and quality of life (QOL). Each interview was conducted by the same researcher to ensure consistency of the questions and methods of interaction. Validated scales, two each for evaluation of sleep and quality of life were used to ensure the consistency of symptoms being reported by the patients.

Sleep

Pittsburgh Sleep Quality Index (PSQI) [19, 20]: PSQI estimates sleep duration, sleep latency, frequency and severity of specific sleep-related problems during the past month [19]. Index comprises 19 items grouped into seven component scores which are scored on a 0 to 3 likert scale. The total score ranges from 0 to 2. Higher scores indicate worse sleep quality.

Medical outcomes study (MOS) 12 item acute revised sleep scale [21, 22]: The MOS sleep scale-R was developed in 2009 as an improvement to original MOS sleep scale. It has six subscale scores (sleep disturbance, snoring, awakening short of breath or with a headache, quantity of sleep, sleep adequacy, and somnolence) and two indexes, sleep problems index I (SPL-I) and sleep problems index II (SPL-II) [21]. Norm-based T scores (mean=50, standard deviation=10) are used to interpret the results. Except for "sleep adequacy" subscale where higher scores reflected more adequate sleep, low scores on MOS sleep scale-R indicated greater sleep problems. The psychometric properties of MOS have been evaluated in patients with neuropathic pain, restless legs syndrome and fibromyalgia [23].

Quality of Life (QOL)

Revised Fibromyalgia Impact Questionnaire (FIQR) [24]: FIQR is a validated version of Fibromyalgia Impact Questionnaire (FIQ) which assesses the functional abilities in daily life. It measures patient's status, progress, and outcomes in context of past 7 days [23, 24]. Composed of 21 items (9 for function, two for overall impact and 10 for symptoms) each

score is rated from 0 to 10. The score for each domain is calculated by summing the scores of corresponding items and dividing it by 3 (for function), 1(for overall impact) and 2 (for symptoms). The score ranges from 0 to 30 for function, 0 to 20 for overall impact and 0 to 50 for symptoms domain respectively. Total score of all three domains ranges from 0 to 100. Higher the scores greater is the global impact of fibromyalgia on the individual's life [25]. The FMS severity was graded depending on the FIQR cut-off values as: ≤30=remission, >30 but ≤45=mild, >46 but ≤65=moderate, >65 severe [26].

Medical outcomes study 36 item Short-Form health survey-36v2™ (SF-36v2) [27]: The SF-36v2 is composed of 36 questions about sociodemographic, health and personal behaviour. It assesses HRQOL comprising eight domains including physical functioning, role limitations because of physical health (role-physical – RP), role limitations because of emotional health (role-emotional – RE)), mental health (MH), social functioning (SF), bodily pain (BP), vitality (VT) and general health (GH) [27]. The scoring was computer based using the quality metric health outcomes™ scoring software 4.5 [28]. Higher scores represent better functioning. Two final measures are used: physical component summary (PCS) and mental component summary (MCS). These scores provide a summary of respondent's health status from both mental health and physical health perspective.

Autonomic Function Tests

Heart Rate Variability measurement: Short term (5 min) HRV measurement was done in all the cases as well as controls. Heart rate variability (HRV) for 5 min was recorded for all the patients by standard methods on power lab (ADInstruments Pt Ltd, Castle Hill Australia) [29]. ECG was sampled at 1,000 Hz and its power spectral analysis was done using fast Fourier transformation (FFT). Both frequency and time domain of the data were analysed. In frequency domain analysis normalized low frequency component (LF nu, 0.04–0.15 Hz) denoting sympathetic activity, normalized high frequency component (HF nu, 0.15–0.4 Hz) denoting parasympathetic activity, LF:HF ratio and total power (TP) were obtained. Time domain analysis was done to obtain – standard deviations of the normal mean RR interval (SDNN), root-mean square of the difference of successive RR intervals (RMSSD) and frequency of two consecutive RR intervals differing by more than 50 ms (pRR50).

Ewing's battery of tests: Standard Ewing's battery of tests was conducted in all the patients of FMS. Sympathetic division was evaluated by (1) Blood pressure (BP) response to sustained handgrip; and (2) BP response to active standing from lying posture while parasympathetic division evaluation included (1) Heart rate response to active standing from the supine posture (30:15 ratio); (2) Heart rate response to Valsalva maneuvers (VM); and (3) Heart rate response to slow deep breathing (expiratory–inspiratory ratio; E:I ratio) [30, 31].

On the basis of Ewing's battery of test patients were classified as "No CAN- if all tests were normal"; "Early CAN- one abnormal heart rate test or two borderline tests" and "Definite CAN- if two tests are abnormal and/or presence of orthostatic hypotension" [30, 31].

Statistical analysis

All the data was systematically recorded and analysed using MS-Excel and SPSS version 16.0 (SPSS Inc, Chicago, IL, USA). The normality of data was tested using Shapiro Wilk test. Unpaired t-test was used for normally distributed data while Mann Whitney U test was used where the distribution of data did not meet norms of normality. Spearman correlation coefficient was used to find the association of sleep parameters with QOL. A two-tailed (α=2), probability value less than 0.05 ($p<0.05$) was considered significant for all statistical tests applied. For multivariate analysis, independent variables AFT which was dichotomous variable (present of absent) and PSQI that demonstrated significant bivariate correlation with the dependent variable FIQR were incorporated into multivariable model. Collinearity was determined by calculating the correlation coefficients and estimating the variance inflation factors of moderately correlated variables.

Results

We enrolled 33 patients of primary fibromyalgia for the study. Three patients did not undergo all the tests thus only 30 patients and 30 age and gender matched controls were finally included in the study (Figure 1). 90 % (n=27) of FMS patients were females with an average age of 40 years, thus both cases as well as controls were relatively young (38.9 ± 10.52, 38.1 ± 10.35 years). FMS patients had mean BMI: 25.38 ± 3.71 kg/m^2 compared to controls with mean BMI 23.85 ± 4.65 kg/m^2 (Table 1). Though, 46.6% (14) patients were overweight and 10% (3) were obese (BMI>30) while 23.3% (7) controls were overweight and 10% (3) were obese. FMS patients had significantly poor sleep quality (13.63 ± 4.15, 3.03 ± 1.56; p=0.0001), increased sleep disturbances (39.46 ± 11, 59.61 ± 2.31; p=0.0001) and they scored poorly on all other sleep parameters of MOS scale (Table 2). The average sleep quantity of FMS patients was 4.63 h which was far less than that of healthy controls (6.86 h).

Sleep and QOL

FMS patients had significantly poor scores of QOL assessed by SF-36V2 for all the domains with least scores for role emotional (32.37 ± 10.93, 53.73 ± 3.05; p=0.0001), bodily pain (33.31 ± 5.31, 58.96 ± 3.94; p=0.0001) and MCS (34.53 ± 9.49, 52.90 ± 3.94; p=0.0001) (Table 3). Correlation analysis of QOL of patients with sleep disturbances, sleep problem index scores (SLP-I and SLP-II) showed significantly positive correlation but showed significant negative correlation with PSQI. Thus, indicating that as the sleep disturbances, SLP-I and SLP-II increase which signify poorer sleep, QOL deteriorates. Also, negative correlation with PSQI suggests that as the sleep quality deteriorates the QOL also goes down (Table 4).

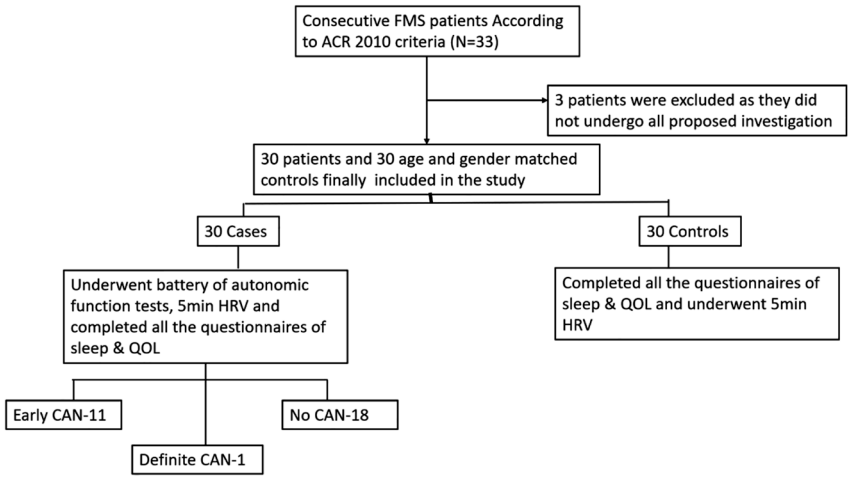

Figure 1: Study flow.

Table 1: Baseline characteristics of the participants.

Variables	Fibromyalgia cases (n=30)	Controls (n=30)	p-Value
Female%, (n)	90% (27)	90% (27)	
Age, years	38.9 ± 10.52	38.1 ± 10.35	0.768
Height, cm	157 ± 6.99	157.20 ± 7.3	0.915
Weight, kg	62.56 ± 9.58	59.31 ± 13.69	0.292
BMI, kg/m^2	25.38 ± 3.71	23.85 ± 4.65	0.164

p<0.05 is significant "*". Unpaired t-test; Data presented as mean ± SD. Shapiro–Wilk test – Age:FMS-0.831, controls-0.974; height:FMS-0.192, controls-0.310; weight-FMS-0.648, controls-0.414.

Table 2: Comparison of the sleep quality by MOS Sleep scale-R and Pittsburgh sleep quality index.

MOS	Fibromyalgia cases (mean ± SD) (n=30)	Controls (mean ± SD) (n=30)	U	p-Value
Slpd	39.46 ± 11	59.61 ± 2.31	56.00	0.0001**
SlpSN	54.97 ± 8.3	58.52 ± 5.04	345.00	0.031*
SOB	43.86 ± 17.08	54.07 ± 3.59	316.50	0.008**
ADQ	44.99 ± 5.77	53.70 ± 6.53	158.00	0.0001**
SM	39.49 ± 7.63	60.95 ± 3.52	0.0001	0.0001**
SLP-1	40.88 ± 6.03	57.33 ± 3.41	11.00	0.0001**
SLP-2	39.11 ± 7.27	59.88 ± 2.55	0.50	0.0001**
PSQI	13.63 ± 4.15	3.03 ± 1.56	5.50	0.0001**

Slpd, Sleep disturbances; SlpSN, Sleep snoring; SOB, Shortness of Breath or Headache; ADQ, Sleep Adequacy; SM, Sleep Somnolence; SLP-1, Sleep Problems Index I; SLP-2, Sleep Problems Index II; PSQI, Pittsburgh sleep quality index. p<0.05 is significant "*". U=Mann Whitney U; Data presented as mean ± SD.

Affect of autonomic dysfunction on QOL and sleep parameters of FMS patients

No differences were seen on short term HRV, comparing autonomic activity of FMS patients and healthy controls (Table 5). Eleven FMS patients had early autonomic dysfunction and one patient had definite autonomic dysfunction but none of the patients had orthostatic hypotension on Ewing's battery of tests. No differences were observed in QOL, sleep quality (PSQI) and other sleep parameters of MOS sleep-R, in patients with autonomic dysfunction and without autonomic dysfunction.

Table 3: Comparison of the quality of life parameters (SF-36v2) of fibromyalgia patients and controls.

Variables	Fibromyalgia cases (mean ± SD) (n=30)	Controls (mean ± SD) (n=30)	U	p-Value
PCS	38.80 ± 5.93	55.76 ± 2.35	0.500	0.0001**
MCS	34.53 ± 9.49	52.90 ± 3.94	22.50	0.0001**
PF	41.97 ± 7.86	55.94 ± 1.88	20.00	0.0001**
RP	35.14 ± 7.98	54.68 ± 2.59	7.00	0.0001**
BP	33.31 ± 5.31	58.96 ± 3.94	0.0001	0.0001**
GH	38.24 ± 8.58	51.26 ± 4.71	102.00	0.0001**
VT	38.43 ± 6.87	57.84 ± 4.45	8.00	0.0001**
SF	37.28 ± 9.76	55.50 ± 3.08	13.50	0.0001**
RE	32.37 ± 10.93	53.73 ± 3.05	31.50	0.0001**
MH	36.39 ± 8.09	52.61 ± 5.20	47.00	0.0001**

PCS, Physical component summary; MCS, Mental component summary; PF, Physical Functioning; RP, Role-Physical; BP, Bodily Pain; GH, General Health; VT, Vitality; SF, Social Functioning; RE, Role-Emotional; MH, Mental Health; p<0.05 is significant "*". U=Mann Whitney U; Data presented as mean ± SD.

Table 4: Correlation of sleep quality and sleep problem index–I and II with physical component summary (PCS) and mental component summary (MCS) of quality of life (SF36v2) among fibromyalgia patients.

Sleep parameters (n=30) QOL domains (n=30)	Sleep Problem Index-I	Sleep Problem Index-II	PSQI
Physical component summary	r=0.484 p=0.007*	r=0.448 p=0.013*	r=−0.416 p=0.022*
Mental component summary	r=0.506 p=0.004*	r=0.526 p=0.003**	r=−0.364 p=0.048*

p<0.05 is significant "*". Data presented as r=Spearman correlation coefficient.

Comparison of sleep measures and QOL among patients of FMS with different grades of severity

Patients of FMS were categorized into 4 grades of severity according to the FIQR grading as: ≤30=remission, >30 but ≤45=mild, >46 but ≤65=moderate, >65 severe [26]. There were 26.7% (8) patients in remission category, 30% (9) in mild category, 40% (12) in moderate and 3.3% (1) in severe category. Further comparisons between QOL and sleep measures were made between two groups: *Group-1 of the remission and mild category patients* while *Group-2 was composed of moderate and severe category*. Significant differences were seen between the two groups with group-1 representing milder form of disease having significantly better sleep (SLP-I:- p=0.003; SLP-II:- p=0.011) and QOL (PCS:- p=0.017; MCS:- p=0.002) (Table 6).

Multivariable linear regression analysis

Age and BMI did not show a linear association with FIQR and thus were not entered in the model (age- r=0.0222; p=0.454: BMI r=−0.069; p=0.359). The outcome variable (FIQR) was normally distributed (Shapiro Wilk statistic-0.964, p=0.401). Analysis of collinearity statistics shows VIF scores as 1.106 and tolerance scores 0.904 respectively for both PSQI and AFT. Our plot of standardised residuals vs. standardised predicted values showed no obvious signs of funnelling, suggesting the assumption of homoscedasticity has been met. The P-P plot for the model suggested that the assumption of normality of the residuals may have been violated. However, as only extreme deviations from normality are likely to have significant impact on findings, the results are probably still valid. Cook's distance values were all under 1, suggesting individual cases were not unduly influencing the model. The multivariable

Table 6: Comparison of sleep measures and quality of life among two groups of patients of fibromyalgia according to disease severity.

Variables	Group-1 (n=17)	Group-2 (n=13)	p-Value (p)
Slpd	42.95 ± 12.03	34.91 ± 7.72	0.045*
SLP-I	43.64 ± 5.67	37.29 ± 4.50	0.003*
SLP-II	41.97 ± 7.06	35.36 ± 5.87	0.011*
PF	44.70 ± 6.92	38.40 ± 7.81	0.027*
RP	37.73 ± 7.73	31.76 ± 7.23	0.04*
BP	35.29 ± 5.66	30.73 ± 3.57	0.017*
GH	42.30 ± 8.08	32.92 ± 6.07	0.002**
VT	41.76 ± 6.12	34.08 ± 5.31	0.001**
SF	42.29 ± 7.30	30.73 ± 8.77	0.001**
RE	37.32 ± 10.15	25.90 ± 8.45	0.003**
MH	39.17 ± 6.28	32.75 ± 8.96	0.029*
PCS	41.00 ± 5.53	35.92 ± 5.34	0.017*
MCS	38.94 ± 7.83	28.76 ± 8.51	0.002**
PSQI	12.47 ± 4.78	15.15 ± 2.60	0.079

PCS, Physical component summary; MCS, Mental component summary; PF, Physical Functioning; RP, Role-Physical; BP, Bodily Pain; GH, General Health; VT, Vitality; SF, Social Functioning; RE, Role-Emotional; MH, Mental Health; Slpd, sleep disturbances; SLP-1, Sleep Problems Index I; SLP-2, Sleep Problems Index II; PSQI, Pittsburgh sleep quality index; p<0.05 is significant "*", p<0.01 is significant "**".

Table 5: Comparison of the heart rate variability parameters of two groups.

HRV	Fibromyalgia cases (Mean ± SD) (n=30)	Controls (Mean ± SD) (n=30)	U	p-Value
LF	58.58 ± 16.76	56.52 ± 16.92	405.00	0.506
HF	40.14 ± 15.97	41.16 ± 16.09	411.00	0.564
LF/HF	2.09 ± 1.98	1.80 ± 1.34	406.00	0.515
SDNN	33.62 ± 12.02	29.57 ± 9.44	349.00	0.135
RMSSD	26.41 ± 14.70	21.78 ± 13.02	350.00	0.139
Total HRV	1,457.19 ± 1,404.72	1,114.60 ± 1,552.61	315.00	0.046

Total HRV, Total power of Heart rate variability; SDNN, standard deviations of the normal mean RR interval; RMSSD, root-mean square of the difference of successive RR intervals; pRR50, 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/HF ratio; p<0.05 is significant "*", p<0.01 is highly significant "**". Data presented as mean ± SD.

regression model with two predictors i.e. PSQI and AFT produced adjusted R^2=0.235, F(2,27)=5.452, p=0.010. This suggests that 23.5% of variance of FIQR can be accounted by PSQI and AFT. Looking at the unique individual contribution of the predictors, the result shows that PSQI positively predicts FIQR (β=0.541, t=3.167, p=0.004) (Table 7). Thus, as sleep quality deteriorates (increased PSQI scores), the severity of FMS increases.

Discussion

Present study explored the association of sleep and autonomic dysfunction with severity of fibromyalgia along with its effect on QOL of FMS patients. FMS patients had significantly reduced sleep duration, significant sleep disturbances and poor sleep quality (p=0.0001). Sleep dysfunction showed significant correlation with poor QOL i.e. increasing sleep disturbances and deteriorating sleep quality had a negative association with QOL (Table 4). Patients with more severe disease registered poorer sleep as well as quality of life (Table 6). Autonomic dysfunction was present only in 12 patients with 11 patients showing early dysfunction. Autonomic dysfunction in FMS patients did not showed any association either with sleep disturbance or with QOL. Further, linear regression confirmed that deteriorating sleep quality significantly increases FMS severity while there is no effect of presence of autonomic dysfunction on FMS severity.

Poor and insufficient sleep has also been suggested as one of the important contributory factors for pathophysiology of FMS [32]. Sleep deprivation even in healthy individuals has been reported to cause myalgia like symptoms [33]. Also, patients of insomnia have been shown to be at an increased risk of development of chronic pain in future [7, 34]. Presence of poor sleep quality in 96.7% (29) of FMS patients in this study compared to only 6.7% (2) controls with poor sleep further suggests the possible role of sleep disturbance in pathogenesis of FMS

Table 7: Multivariable linear regression results.

Variables	Unstandardized coefficients		β	p-Value
	b	Std. Error		
Constant	13.592	9.989		0.185
PSQI	2.041	0.644	0.541**	0.004
AFT	0.497	5.38	0.016	0.927

PSQI, Pittsburgh sleep quality index; AFT, Autonomic Function Test (0 – Normal, 1 – Abnormal). *p<0.05; **p<0.01.

[35]. Liedberg et al. classified FMS patients as good or bad sleepers and reported that bad sleepers had greater pain, poorer QOL, fatigue and disability [36]. They suggested that assessing and addressing sleep problems was clinically important for a better treatment outcome, though they did not used a validated sleep questionnaire. In another large population based prospective study by Mork and Nilsen, sleep problems were associated with a greater risk of developing FMS [37]. But they assessed sleep problems by a single question and also they did not assessed all FMS cases based on recommended diagnostic criteria. However, in our study we used latest ACR 2010 diagnostic criteria as well as more comprehensive tools to assess sleep problems. We also found that total sleep duration was notably less and sleep quality was significantly poor along with increased sleep disturbances in patients with FMS. Interestingly, sleep abnormalities increases with FMS severity, and decreasing sleep quality further predicts increase in FMS severity (Table 7) [38]. Our study highlights that pain and sleep have a significant association however; presence of covariates like anxiety and depression may also have a contributory role which is considered to co-exist with sleep derangements [39].

QOL which is defined as "an individual's perception of their position in life in context of the culture and value system of which they live with the relation to their goals, expectations, standards and concerns" [40]. General population surveys of various pain conditions like rheumatoid arthritis, osteoarthritis, SLE, migraine and FMS have shown that people in each pain condition had significantly low scores but patients with FMS had most prominent impairments in QOL [41]. Wagner et al. have shown that sleep difficulty symptoms are independently (even after controlling pain) associated with decrements in mental and physical health related QOL of FMS patients [7]. These observations suggest that pain is not the only factor responsible for poor QOL in FMS and other covariates may have contributory role [42]. In our study, FMS patients had poor QOL and it deteriorated with deterioration of sleep and with the increasing impact of FMS which includes pain (Table 3). Present study supports the supposition of a complex bidirectional relationship of pain and poor sleep [43, 44]. Studies have shown complex mediation of pain-depression pathway by treating sleep while others have demonstrated pain as a mediator of sleep and depressive symptoms [45, 46]. Thus, present study supports the view that both sleep and pain should be addressed in patients of FMS with poor QOL.

Evaluation of HRV did not revealed any difference between patients and controls. However, a trend of low parasympathetic and higher sympathetic activity was

noted among patients. Though, no association could be observed between FMS severity and HRV parameters in this study. Autonomic reactivity test by Ewing's battery did not reveal much and only 1 patient had definite CAN while 11 patients had early CAN. Conflicting reports are present in literature regarding autonomic dysfunction in FMS. Few have reported consistent sympathetic hyperactivity at rest and hypo-reactivity to stressful stimuli while other studies have reported a normal autonomic resting tone in FMS [47, 48]. A study in Indian population has shown that FMS patients show autonomic reactivity comparable to healthy controls which is consistent with the findings of present study [48]. Interestingly, Vincent et al. have also reported that patients with moderate grade of FM severity may not have clinically significant levels of autonomic dysfunctions [14], whereas, Martinez-Lavin found a deranged sympathetic response to an active orthostatic stress compared to controls [10]. They reported a diminished 24 h HRV due to an increased nocturnal predominance of LF band oscillations consistent with an exaggerated sympathetic modulation. Nocturnal HRV indices have been considered as potential FMS biomarkers [49]. However, present study did not reveal any differences in either QOL, sleep quality or sleep disturbances of FMS patients with or without autonomic dysfunctions. Sleep centre and autonomic regulatory centres though are in proximity and both may be involved with progression of disease. However, at this juncture we are not able to comment on the simultaneous affliction of the two centres. One of the possible explanations for non-association of autonomic function dysregulation in our patients at this stage may be due to less severe FMS in them.

This study gives an important insight that sleep dysfunction plays a greater role in effecting the QOL of FMS patients with mild disease compared to autonomic dysfunction. However, present study too is not without limitations. As it was a cross sectional study, a cause and effect relationship could not be assessed between sleep, pain and autonomic dysfunction in FMS patients. Future longitudinal follow up study with a larger sample size should be done to explore the causal association of pain, sleep and autonomic dysfunction including polysomnography to assess the objective sleep parameters as well.

Conclusions

Etiopathogenesis of FMS is still ambiguous. Autonomic dysfunction is postulated as a potential mechanism associated with pain in FMS while pain has been shown to have a reciprocal relationship with sleep. Sleep is important for maintaining physiological homeostasis yet, it is a commonly overlooked drive. Present study highlights that FMS patients have wide spectrum of sleep disturbances ranging from reduced sleep duration to poor sleep quality. Deteriorated sleep showed a negative association with FMS severity as well as QOL. Autonomic dysfunction, on the other hand, did not show any association with severity of FMS. Thus, present study concludes that full spectrum of sleep disturbances and sleep quality should be explored in patients of FMS.

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References

1. Bennett RM, Jones J, Turk DC, Russell IJ, Matallana L. An internet survey of 2,596 people with fibromyalgia. BMC Musculoskelet Disord 2007;8:27.
2. Queiroz LP. Worldwide epidemiology of fibromyalgia. Curr Pain Headache Rep 2013;17:356.
3. Berger A, Dukes E, Martin S, Edelsberg J, Oster G. Characteristics and healthcare costs of patients with fibromyalgia syndrome. Int J Clin Pract 2007;61:1498–508.
4. Bradley LA. Pathophysiology of fibromyalgia. Am J Med. 2009; 122:S22–30.
5. Junior MH, Goldenfum MA, Siena CA. Fibromyalgia: clinical and occupational aspects. Rev Assoc Med Bras (English Ed) 2012;58: 358–65.
6. Kleinman L, Mannix S, Arnold LM, Burbridge C, Howard K, McQuarrie K, et al. Assessment of sleep in patients with fibromyalgia: qualitative development of the fibromyalgia sleep diary. Health Qual Life Outcome 2014;12:111.
7. Wagner JS, DiBonaventura MD, Chandran AB, Cappelleri JC. The association of sleep difficulties with health-related quality of life among patients with fibromyalgia. BMC Musculoskelet Disord 2012;13:199.
8. Calandra-Buonaura G, Provini F, Guaraldi P, Plazzi G, Cortelli P. Cardiovascular autonomic dysfunctions and sleep disorders. Sleep Med Rev 2016;26:43–56.
9. Miglis MG. Autonomic dysfunction in primary sleep disorders. Sleep Med 2016;19:40–9.
10. Martinez-Lavin M. The autonomic nervous system and fibromyalgia. J Muscoskel Pain 2002;10:221–8.

11. Cohen H, Neumann L, Kotler M, Buskila D. Autonomic nervous system derangement in fibromyalgia syndrome and related disorders. Isr Med Assoc J 2001;3:755–60.
12. Elam M, Johansson G, Wallin BG. Do patients with primary fibromyalgia have an altered muscle sympathetic nerve activity?. Pain 1992;48:371–5.
13. Cohen H, Neumann L, Alhosshle A, Kotler M, Abu-Shakra M, Buskila D. Abnormal sympathovagal balance in men with fibromyalgia. J Rheumatol 2001;28:581–9.
14. Vincent A, Whipple MO, Low PA, Joyner M, Hoskin TL. Patients with fibromyalgia have significant autonomic symptoms but modest autonomic dysfunction. PM&R 2016;8:425–35.
15. Yunus MB. The prevalence of fibromyalgia in other chronic pain conditions. Pain Res Treat 2012;2012:584573.
16. Assumpção A, Pagano T, Matsutani LA, Ferreira EA, Pereira CA, Marques AP. Quality of life and discriminating power of two questionnaires in fibromyalgia patients: fibromyalgia impact questionnaire and medical outcomes study 36-item short-form health survey. Braz J Phys Ther 2010;14:284–9.
17. Kwiatek R. Treatment of fibromyalgia. Aust Prescr 2017;40:179.
18. Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Katz RS, Mease P, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. Arthritis Care Res 2010;62:600–10.
19. Buysse DJ, Reynolds CF III, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatr Res 1989;28:193–213.
20. Manzar MD, Moiz JA, Zannat W, Spence DW, Pandi-Perumal SR, BaHammam AS, et al. Validity of the Pittsburgh sleep quality index in Indian university students. Oman Med J 2015;30:193.
21. Hays RD, Stewart AL. Sleep measures. In: Stewart AL,Ware JE, editors. Measuring functioning and well-being: the Medical Outcomes Study Approach. Durham (NC): Duke University Press; 1992:p. 235–59.
22. Martin S, Chandran A, Zografos L, Zlateva G. Evaluation of the impact of fibromyalgia on patients' sleep and the content validity of two sleep scales. Health Qual Life Outcome 2009;7:64.
23. Sadosky A, Dukes E, Evans C. Reliability of a 1-week recall period for the Medical Outcomes Study Sleep Scale (MOS-SS) in patients with fibromyalgia. Health Qual Life Outcome 2009;7:12.
24. Bennett RM, Friend R, Jones KD, Ward R, Han BK, Ross RL. Revised Fibromyalgia Impact Questionnaire (FIQR): validation & psychometric properties. Arthritis Res Ther 2009;11:R120.
25. Burckhardt CS, Clark SR, Bennett RM. The fibromyalgia impact questionnaire: development and validation. J Rheumatol 1991;18: 728–33.
26. 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: 1074–81.
27. Ware JE, Kosinski M, Bjorner JB, Turner-Bowker DM, Gandek B, Maruish ME. User's manual for the SF-36v2 Health Survey, 2nd ed. Lincoln. RI: QualityMetric Incorporated; 2007.
28. Ware JE, Kosinski M, Dewey JE. How to score version 2 of the SF-36 health survey (standard & acute forms). QualityMetric Incorporated; 2000.
29. Malik M, Camm AJ, Bigger JT, Breithardt G, Cerutti S, Cohen RJ, et al. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Eur Heart J 1996;17: 354–81.
30. Sharma RK, Deepak KK, Bijlani RL, Rao PS. Short-term physical training alters cardiovascular autonomic response amplitude and latencies. Indian J Physiol Pharmacol 2004;48:165–73.
31. Ewing DJ, Martyn CN, Young RJ, Clarke BF. The value of cardiovascular autonomic function tests: 10 years experience in diabetes. Diabetes Care 1985;8:491–8.
32. Lentz MJ, Landis CA, Rothermel JS, Shaver JL. Effects of selective slow wave sleep disruption on musculoskeletal pain and fatigue in middle aged women. J Rheumatol 1999;26:1586–92.
33. Generaal E, Vogelzangs N, Penninx BW, Dekker J. Insomnia, sleep duration, depressive symptoms, and the onset of chronic multisite musculoskeletal pain. Sleep 2017;40. https://doi.org/10.1093/sleep/zsw030.
34. Mundal I, Gråwe RW, Bjørngaard JH, Linaker OM, Fors EA. Psychosocial factors and risk of chronic widespread pain: an 11-year follow-up study—the HUNT study. Pain 2014;155: 1555–61.
35. Bigatti SM, Hernandez AM, Cronan TA, Rand KL. Sleep disturbances in fibromyalgia syndrome: relationship to pain and depression. Arthritis Care Res 2008;59:961–7.
36. Liedberg GM, Björk M, Börsbo B. Self-reported nonrestorative sleep in fibromyalgia–relationship to impairments of body functions, personal function factors, and quality of life. J Pain Res 2015;8:499.
37. Mork PJ, Nilsen TI. Sleep problems and risk of fibromyalgia: longitudinal data on an adult female population in Norway. Arthritis Rheum 2012;64:281–4.
38. Lautenbacher S, Kundermann B, Krieg JC. Sleep deprivation and pain perception. Sleep Med Rev 2006;10:357–69.
39. Rizzi M, Radovanovic D, Santus P, Airoldi A, Frassanito F, Vanni S, et al. OP0006 Influence of autonomic nervous system dysfunction in the genesis of sleep disorders in fibromyalgia patients.
40. Whoqol Group. The World Health Organization quality of life assessment (WHOQOL): position paper from the World Health Organization. Soc Sci Med 1995;41:1403–9.
41. Strömbeck B, Ekdahl C, Manthorpe R, Wikström I, Jacobsson L. Health-related quality of life in primary Sjögren's syndrome, rheumatoid arthritis and fibromyalgia compared to normal population data using SF-36. Scand J Rheumatol 2000;29: 20–8.
42. Di Venere D, Corsalini M, Stefanachi G, Tafuri S, De Tommaso M, Cervinara F, et al. Quality of life in fibromyalgia patients with craniomandibular disorders. Open Dent J 2015;9:9.
43. Jansson-Fröjmark M, Boersma K. Bidirectionality between pain and insomnia symptoms: a prospective study. Br J Health Psychol 2012;17:420–31.
44. O'Brien EM, Waxenberg LB, Atchison JW, Gremillion HA, Staud RM, McCrae CS, et al. Intraindividual variability in daily sleep and pain ratings among chronic pain patients: bidirectional association and the role of negative mood. Clin J Pain 2011;27: 425–33.
45. Hamilton NA, Pressman M, Lillis T, Atchley R, Karlson C, Stevens N. Evaluating evidence for the role of sleep in fibromyalgia: a test of the sleep and pain diathesis model. Cognit Ther Res 2012;36: 806–14.

46. Miró E, Martínez MP, Sánchez AI, Prados G, Medina A. When is pain related to emotional distress and daily functioning in fibromyalgia syndrome? The mediating roles of self-efficacy and sleep quality. Br J Health Psychol 2011;16: 799–814.
47. Staud R. Heart rate variability as a biomarker of fibromyalgia syndrome. Future Rheumatol 2008;3:475.
48. Kulshreshtha P, Gupta R, Yadav RK, Bijlani RL, Deepak KK. A comprehensive study of autonomic dysfunction in the fibromyalgia patients. Clin Auton Res 2012a;22:117–22.
49. Lerma C, Martinez A, Ruiz N, Vargas A, Infante O, Martinez-Lavin M. Nocturnal heart rate variability parameters as potential fibromyalgia biomarker: correlation with symptoms severity. Arthritis Res Ther 2011;6:R185.