

# Depression, sexuality and fibromyalgia syndrome: clinical findings and correlation to hematological parameters

Depressão e sexualidade na síndrome fibromiálgica: achados clínicos e correlação com parâmetros hematológicos

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## ABSTRACT

Fibromyalgia (FM) is characterized by chronic pain and comorbidities. **Objective:** To investigate sexuality and depression in women with FM compared with controls and to correlate the findings with hematological parameters. **Methods:** 33 women with FM and 19 healthy women were included and evaluated with the following instruments: Female Sexual Function Index, Beck Inventory, Visual Analogue Scale, medical history and laboratory exams. **Results:** The prevalence of sexual dysfunction ( $P = 0.007$ ) and depression ( $P < 0.001$ ) were higher in the study group than in the control group; they were positively correlated ( $P = 0.023$ ). The study group showed lower serum concentrations of testosterone, free T4, antinuclear factor, and lower blood hemoglobin and hematocrit. **Conclusions:** FM was associated with high scores of sexual dysfunction and depression, and there were correlations with hematological parameters. We suggest the involvement of immune-inflammatory mediators and FM, which need further investigation to understand their role in FM syndrome and its comorbidities.

**Keywords:** fibromyalgia; depression; sexuality; hematologic tests

## RESUMO

Fibromialgia (FS) é caracterizada por dor e comorbidades. **Objetivo:** investigar depressão e sexualidade em mulheres com FS comparadas a controles, e correlacionar os achados com parâmetros hematológicos. **Métodos:** 33 mulheres com FS e 19 controles saudáveis foram incluídas e avaliadas através dos seguintes instrumentos: Índice de Função Feminina Sexual, Inventário de Beck, escala visual analógica, história médica e exames laboratoriais. **Resultados:** A prevalência de disfunção sexual ( $P = 0,007$ ) e depressão ( $P < 0,001$ ) foram maiores no grupo de estudo do que nos controles; também houve correlação positiva ( $P = 0,023$ ). O grupo de estudo apresentou menor concentração sérica de testosterona, T4 livre, fator antinuclear e menos concentração de hemoglobina e hematócrito. **Conclusões:** A FS associou-se com altos índices de disfunção sexual e depressão, e houve correlação com os parâmetros hematológicos estudados. Sugere-se o envolvimento de mediadores imuno-inflamatórios na FS, que necessita de maior investigação para a compreensão dos mecanismos tanto na FS e quanto em suas comorbidades.

**Palavras-chaves:** fibromialgia; depressão; sexualidade; testes hematológicos.

Fibromyalgia (FM) is characterized by generalized pain, decreased pain thresholds, sleep disturbances, fatigue, edema, paresthesia and dysesthesia, morning stiffness with a short duration, psychological distress and chronic headache. It is often associated with articular and muscular pain, and inflammation<sup>1</sup>. There is a high prevalence of FM in adult women (4-7 times more common in women between 30 and 60 years old than in men or other ages)<sup>2</sup>.

The pathophysiology of FM is not yet clear<sup>2,3</sup>. It includes neurophysiological mechanisms such as altered

concentrations of substance P, dynorphin and nerve growth factor in the cerebrospinal fluid, altered blood concentration of neuropeptide Y<sup>1</sup>, sensory abnormalities, altered NMDA receptors, deficit in the inhibitory pain system and other neurological disturbances<sup>2</sup>. Inflammatory observations show high serum concentrations of interleukin 10 (IL-10), IL-8 and tumoral necrosis factor (TNF $\alpha$ ), correlated with clinical parameters<sup>3</sup>. Cytokines are associated with pain because of their role in central sensitization, which suggest their influence in FM and depression<sup>3</sup>.

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Fibromyalgia patients have also sexual dysfunction<sup>1,4,5,6</sup> and reproduction problems<sup>5</sup>, as well as depression<sup>7</sup>. The mechanisms are unclear but seem to involve the hypothalamus-pituitary-adrenal axis, sexual hormones and cytokines<sup>8</sup>. Depression affects the life of 83.3% patients with FM<sup>9</sup> and, in Brazil, 67.2% of them have depression diagnosed as a comorbidity<sup>10,11,12</sup>. Thus, the objectives of this study were to investigate the sexuality and depression in women with FM compared with controls, and to correlate the clinical findings to blood parameters.

## METHODS

Thirty-three ( $n = 33$ ) women consecutively diagnosed as having FM in the period between November 2009 and September 2010 were included and evaluated in this study. They were compared to 19 healthy women (control group). The patients had been diagnosed at the Physical Medicine Division, Trauma and Orthopedic Institute, Hospital das Clínicas, Medical School, University of Sao Paulo, and had fulfilled the criteria of the American College of Rheumatology: chronic widespread pain (duration longer than six months), and at least 11 out of 18 possible tender points (widespread pain is defined as axial pain plus upper and lower segment plus left- and right-sided pain)<sup>13</sup>.

The patients were instructed to keep taking their medication during the evaluation period, which they had been taking during the previous six months with no variation in doses. All women were informed about the purposes of this study and signed the informed consent. The project was previously approved by the local Ethics Committee.

Inclusion criteria of the study group: women with the diagnosis of FM according to the American College of Rheumatology criteria and more than six months of pain.

Inclusion criteria of the control group: healthy women with no complaint of pain during the last 12 months and no use of chronic medication.

*Exclusion criteria of both groups:* inflammatory or rheumatologic comorbidities (eg. rheumatoid arthritis, lupus erythematosus), diabetes mellitus, neurological diseases and hypothyroidism.

### Investigation of tender points

The tender points exam was performed at the time of diagnosis on the day of the investigation, in all subjects by one observer (H.K.). A tender point was counted as "positive" if the pressure pain threshold was lower than 393kPa ( $4\text{kg}/\text{cm}^2$ )<sup>13</sup>. An electronic pressure algometer (Somedic, Sweden) with a probe area of  $1\text{cm}^2$ , which was pressed on the skin with a ramp rate of  $50\text{kPa}/\text{s}$ , was used to determine the pressure pain threshold over the designated tender point areas. Tenderness at any point was considered if some involuntary verbal or facial expression of pain occurred or

withdrawal was observed. All patients presented with at least 11 tender points, fulfilling the American College of Rheumatology criteria<sup>13</sup>.

The evaluation consisted of the following questionnaires, instruments of evaluation and examinations: (a) female sexual function index validated to the Portuguese language<sup>14</sup>; (b) beck inventory for the evaluation of depression, validated to the Portuguese language<sup>15</sup>; (c) visual analogue scale (only for the study group); (d) demographic data; (e) medical profile with data on the disease (pain characteristics, clinical exam, comorbidities); (f) laboratory exams: blood samples (5 mL) were collected for serum analysis of the concentration of the following substances: antinuclear factor, immunoglobulins (IgM, IgG, IgE), total proteins and fractions, rheumatoid factor, circulating immune complexes, complement factors C3 and C4, reactive C protein, complete hemogram with red and white series, platelets, albumin, globulin, thyroid-stimulating hormone (TSH), tetraiodothyronine (T4), free T4, triiodothyronine (T3), luteinizing hormone (LH), follicle-stimulating hormone, prolactin, estrogen, progesterone, testosterone, serum cortisol, and adrenocorticotrophic hormone (ACTH).

### Statistical analysis

The sample size was calculated with a confidence interval of 95% comparing the prevalence of FM and correlated comorbidities at the pain clinic. All data were tabled and the frequencies and percentages, means, standard deviations and ranges were compared among the groups. After the initial descriptive evaluation, variables were tested around normal distribution with the Shapiro-Wilk test and Q-Q plots. For quantitative variables with normal distribution we used ANOVA 1 factor. Post hoc comparisons were calculated using the Tukey test. Non-parametric tests included Pearson's chi-square and Fisher's exact test. Correlations among the variables were tested with Pearson's. All statistical calculations were performed using SPSS 17.0 (SPSS Inc., Illinois, USA). The level of significance was 5%.

## RESULTS

The mean ages were 39.73 years (study group) and 30.79 years (control group). Statistical differences were found in ages, educational status and work activity (Table 1). The study group had higher serum concentrations of C4, T4, T3, rheumatoid factor and C-reactive protein (CRP) than the controls; the study group showed lower serum concentrations of testosterone, free T4, antinuclear factor, and lower blood hemoglobin and hematocrit than the control group (Table 2; Figures 1 and 2).

There were higher scores of sexual dysfunction (ANOVA,  $p < 0.001$ ) and depression (ANOVA,  $p < 0.001$ ) in the study group than the control group (Figures 3 and 4). The prevalence

of sexual dysfunction (chi-square  $p = 0.007$ ) and depression ( $p < 0.001$ ) were higher in the study group than the control group as well. High sexual dysfunction was also correlated with depression ( $p = 0.023$ ).

The following correlations were also observed in both groups: high depression with low concentration of antinuclear factor ( $p = 0.048$ ) and IgG ( $p = 0.035$ ); high sexual dysfunction with low concentrations of luteinizing hormone ( $p = 0.031$ ), follicular stimulant hormone ( $p = 0.001$ ) and platelets ( $p = 0.002$ ).

In the study group, high depression was correlated to high sexual dysfunction ( $p = 0.003$ ), high pain intensity on the Visual Analogue Scale ( $p = 0.005$ ), high ACTH ( $p = 0.046$ ) levels, high progesterone levels ( $p = 0.042$ ), low C3 ( $p = 0.019$ ) and low mean corpuscular volume in the blood count ( $p = 0.034$ ). Other correlations were: high pain intensity to high C3 and low IgM ( $p = 0.019$ ); high age to high estradiol ( $p = 0.033$ ) and cortisol ( $p = 0.026$ ). Menopause was associated with low concentration of rheumatoid factor ( $p = 0.008$ ) and sexual dysfunction was associated with low levels of leucocytes ( $p = 0.029$ ).

**Table 1.** Demographic and general comparison between the study group and the control group ( $n = 52$ ).

Variable	Study Group (n = 33)	Control Group (n = 19)	P*
Ages (years)	39.73 ± 6.31 (29–49)	30.79 ± 8.43 (21–48)	0.000
Educational status (%)			
Less than high school	39.4	15.8	0.001
Completed high school	57.6	47.4	
Completed undergraduation	3.0:	36.8	
Marital status (%)			
Single	9.1	57.9	0.052
Married	75.7	31.6	
Divorced	15.2	10.5	
Work activity (%)			
Yes	39.4	78.9	0.005
Menopause (%)	3.0	5.3	0.694
Hormonal replacement (%)	0.0	0.0	-
Contraceptive use (%)	21.2	10.5	0.314

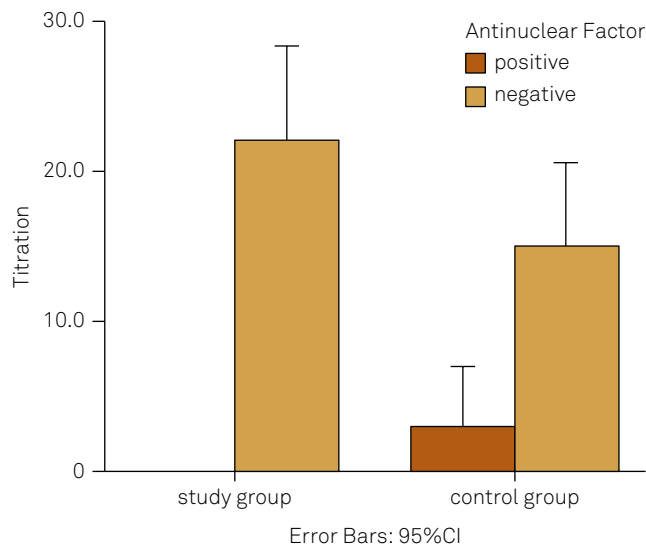
\*oneway ANOVA.

**Table 2.** Results of blood sample analysis: comparison between the study group and the control group ( $N = 52$ ).

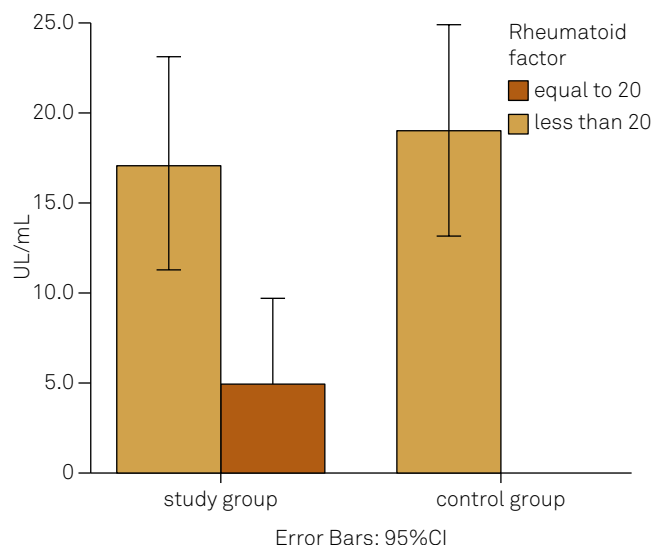
Variable	Study group ( $n = 33$ )	Control group ( $n = 19$ )	p**
ACTH* (pg/ml)	$15.2 \pm 6.7$ (5.0–33.0)	$16.8 \pm 15.0$ (4.0–67.0)	0.657
C3 (mg/dL)	$134.3 \pm 36.6$ (8.2–194.0)	$117.8 \pm 18.5$ (91.0–157.0)	0.083
C4 (mg/dL)	$26.8 \pm 8.2$ (13–48)	$22.0 \pm 5.8$ (10.9–32.4)	0.038
Estradiol (pg/mL)	$67.3 \pm 49.8$ (13.0–172.0)	$85.8 \pm 89.2$ (13.0–267.1)	0.393
Progesterone (pg/mL)	$4.0 \pm 8.3$ (0.3–34.0)	$2.7 \pm 4.7$ (0.3–15.8)	0.554
LH (pg/mL)	$13.9 \pm 18.3$ (0.6–56.2)	$10.0 \pm 11.8$ (0.1–48.0)	0.420
FHS (pg/mL)	$26.1 \pm 38.4$ (1.4–136.6)	$13.4 \pm 22.0$ (0.6–80.5)	0.213
Prolactin (pg/mL)	$11.9 \pm 19.8$ (2.5–98.7)	$13.3 \pm 7.6$ (4.5–29.3)	0.782
Testosterone (pg/mL)	$15.8 \pm 8.3$ (10.1–40.0)	$27.52 \pm 15.08$ (12–0–57.0)	0.003
TSH ( $\mu$ U/mL)	$2.9 \pm 2.2$ (0.5–8.1)	$1.8 \pm 0.9$ (0.9–4.4)	0.072
T4 ( $\mu$ g/dL)	$9.1 \pm 1.5$ (6.5–12.7)	$8.0 \pm 1.8$ (5.6–14.0)	0.040
Free T4 ( $\mu$ g/dL)	$0.9 \pm 0.1$ (0.7–1.2)	$1.2 \pm 0.2$ (1.0–1.5)	0.000
T3 (pg/dL)	$145.3 \pm 24.7$ (98.0–197.0)	$119.2 \pm 28.5$ (76.0–194.0)	0.003
Cortisol ( $\mu$ g/dL)	$8.9 \pm 3.8$ (1.6–17.2)	$10.0 \pm 5.5$ (3.3–21.4)	0.419
Hemoglobin (g/dL)	$12.9 \pm 1.2$ (9.5–15.4)	$13.7 \pm 1.2$ (10.4–15.4)	0.059
Hematocrit (%)	$38.7 \pm 3.2$ (31.5–44.6)	$41.0 \pm 3.3$ (31.5–45.2)	0.034
Mean corpuscular volume (%)	$81.8 \pm 23.7$ (8.1–96.8)	$89.6 \pm 3.7$ (79.3–96.7)	0.167
Mean corpuscular hemoglobin (%)	$29.6 \pm 2.4$ (23.6–32.5)	$29.8 \pm 1.5$ (26.2–31.9)	0.747
Mean corpuscular hemoglobin concentration (%)	$33.3 \pm 1.4$ (30.2–35.7)	$33.3 \pm 1.1$ (31.1–35.8)	0.965
Red cell distribution width (uug)	$13.6 \pm 1.1$ (11.8–16.0)	$13.3 \pm 0.6$ (12.3–14.9)	0.200
Platelets (ml/mm <sup>3</sup> )	$268.1 \pm 58.7$ (170.0–343.0)	$269.6 \pm 45.0$ (187.0–352.0)	0.936
CRP (mg/L)	$7.0 \pm 7.5$ (0.3–32.6)	$1.7 \pm 1.6$ (0.2–5.3)	0.005
IgE (UI/mL)	$88.1 \pm 110.9$ (6.0–472.0)	$104.3 \pm 117.8$ (5.0–413.0)	0.681
IgG (UI/mL)	$1183.6 \pm 221.1$ (801.0–1545.0)	$1168.9 \pm 124.6$ (981.0–1459.0)	0.808
IgM (UI/mL)	$111.1 \pm 71.5$ (48.5–358.1)	$130.5 \pm 38.7$ (60.2–199.4)	0.324
Total protein (g/dL)	$7.3 \pm 0.4$ (6.5–8.1)	$7.2 \pm 0.3$ (6.8–7.9)	0.583
Leucocytes (mil mm <sup>3</sup> )	$7.285.9 \pm 1.939.1$ (2.9–12.3)	$7.847.4 \pm 2.417.9$ (4.7–14.2)	0.414

\*ACTH: adrenocorticotrophic hormone; C3: complement factor 3; C4: complement factor 4; LH: luteinizing hormone; IgE: immunoglobulin E; IgG: immunoglobulin G; IgM: immunoglobulin M; FSH: follicle-stimulating hormone; CRP: C-reactive protein; TSH: thyroid stimulant hormone; T3: triiodothyronine; T4: tetraiodothyronine.

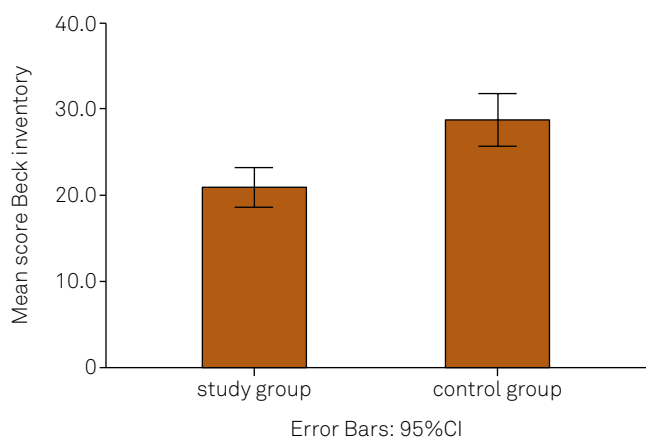
\*\*oneway ANOVA; Bold means significant; Results are presented in Mean  $\pm$  Standard Deviation (Minimum-Maximum).



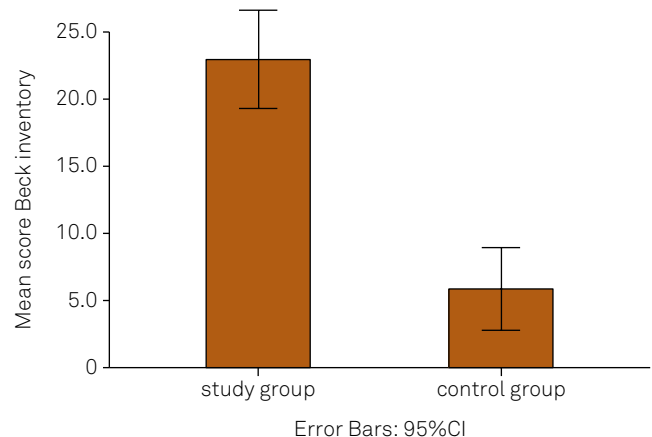
**Figure 1.** Antinuclear factor: comparison between the study and control groups ( $p = 0.048$ ).



**Figure 2.** Rheumatoid factor: comparison between the study and control groups ( $p = 0.027$ ).



**Figure 3.** Mean sexual dysfunction scores: comparison between the study and control groups ( $p = 0.000$ ).



**Figure 4.** Mean depression scores: comparison between the study and control groups ( $p = 0.000$ ).

## DISCUSSION

This study showed a significant association between sexual dysfunction and depression in FM patients. Sexual dysfunction can interfere in the quality of life and aggravate FM symptoms and depression, a frequent comorbidity of FM. The pathophysiological mechanisms seem to involve the peripheral and central nervous systems, hormones and/or immune-inflammatory mediators<sup>4,8,9</sup>, and hormonal variation associated with stress and the climacteric syndrome<sup>16,17</sup>. The search for clinical evidence is necessary to understand the role of comorbidities in FM and new possible approaches to assess these patients.

Sexual dysfunction and depression are important comorbidities that aggravate the clinical picture and reduce the quality of life of patients with FM. The treatment of chronic pain is complex and interdisciplinary, and the assessment of associated conditions is crucial to improve pain alleviation

and to rehabilitate the patient, thus avoiding a new pain crisis<sup>11,12,18</sup>. Symptomatic treatment needs to be followed by other non-pharmacological strategies, such as physiotherapy, psychotherapy, and the adaptation of the patient to general daily activities, leisure and work<sup>5</sup>. Previous studies support our findings, but the mechanisms that are underlying these associations are lacking<sup>6,7</sup>. Studies with longitudinal designs would also contribute to the understanding of case-effect factors. The current knowledge of the biological background will be discussed.

Fibromyalgia is associated with an increase in inflammatory activity<sup>18,19</sup>, which is supported by the higher concentration of CRP, rheumatoid factor and complement in patients than in controls. It is known that cytokines such as IL-1 $\beta$ , TNF- $\alpha$  and IL-6 can trigger the inflammatory activity of FM<sup>3,19</sup>, and hormonal/neuronal mechanisms are probably behind this. Inflammatory mediators and cytokines can act in bone marrow and increase the production of blood

cells, resulting in high hematocrit and blood hemoglobin, as observed in this study<sup>20,21</sup>. As well, they act in hepatocytes, altering CRP, rheumatoid factor, and complement concentrations<sup>21,22,23</sup>. The pain intensity was high in patients who had a high concentration of ACTH and C3 and low concentration of immunoglobulins, which suggests a cellular immune process mediated by T cells. These are cytokine releasers that are found to be activated in FM<sup>3,19,20,21,22,23</sup>.

The role of hormones in FM has been investigated, and the decline of sexual hormones in the climacteric syndrome could even be a potential etiology for FM<sup>17</sup>. Hormones are found to be altered in FM patients and they have direct influence in neurological and immunological functioning. ACTH and cortisol levels are linked to stress, pain and depression<sup>20</sup>, and were altered in this sample. This could indicate an imbalance of feedback mechanisms of stress and inflammation<sup>16,19,20,21,22</sup>, although the activation or suppression of the hypothalamus-pituitary-adrenal axis in FM remains controversial<sup>23,24</sup>. Besides the activation of the hypothalamus-pituitary-adrenal axis, there are low concentrations of dehydroepiandrosterone in FM patients<sup>25</sup>.

Testosterone was another hormone that we found in lower concentration in the study group than the control group, and it is known that low levels of testosterone may play a role in sexual dysfunction and depression in FM<sup>26,27</sup>.

Although the subjects included in this sample did not have thyroid diseases, there was a statistical difference in the concentration of thyroid hormones between the groups and this may play a role in pain and emotional comorbidities<sup>28</sup>. Besides the neurological and inflammatory mechanisms involved in FM, hormonal abnormalities should be considered in the pathophysiological process, or even as an etiology for FM. They could be targets to improve pain and its comorbidities in this complex syndrome, although a study with dehydroepiandrosterone for FM showed negative results<sup>29</sup>.

A limitation of this study was the age differences between the groups, which could influence the results. It is known that there is a decline in sexual hormones with aging, especially after menopause, and other findings from laboratory tests may be altered by this age.

In conclusion, the study group had higher scores of sexual dysfunction and depression ( $p < 0.001$ ) than the controls, and their prevalence was also higher ( $p = 0.007$  and  $p = 0.001$  respectively). Fibromyalgia was associated with high serum concentrations of C4, T4, T3, rheumatoid factor and CRP, high blood hemoglobin and hematocrit, and low testosterone, free T4, and antinuclear factor. This study shows evidence of inflammatory activity in FM patients, which needs further investigation to understand the role of these findings in the pathophysiological mechanisms of this disease and in its comorbidities.

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