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## Brief communication

# Effects of physical exercise on serum levels of serotonin and its metabolite in fibromyalgia: a randomized pilot study

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## ABSTRACT

To evaluate the effects of aerobic training and stretching on serum levels of serotonin (5HT) and its main metabolite 5-hydroxyindolacetic acid (5HIAA).

Twenty-two women with FM were randomized into one of two exercise modalities (aerobic walking exercise or stretching exercise) to be accomplished three times a week for 20 weeks. The serum levels of 5HT and 5HIAA were evaluated before and after the exercise program by high performance liquid chromatography (HPLC) with colorimetric detection.

Within group analysis (pre-post) showed that serum levels of both 5HT and 5HIAA changed significantly in the aerobic group during the 20-week course of therapy (5HT:  $P = 0,03$ ; 5HIAA:  $P = 0,003$ ). In the stretching group, however, no statistically significant change was observed (5HT:  $P=0,491$ ; 5HIAA:  $P=0,549$ ). Between group statistical comparisons of laboratory measures disclosed that aerobic training was superior to stretching in that it significantly increased the levels of 5HIAA (F test = 6.61;  $P = 0.01$ ), but the average difference between groups on the levels of 5HT did not meet significance criteria (F test = 3.42;  $P = 0.08$ ). Aerobic training increases the 5HIAA and 5HT levels and it could explain why aerobic exercise can improve symptoms in fibromyalgia syndrome patient more than stretching exercise.

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## Efeitos do exercício físico sobre os níveis séricos de serotonina e seu metabólito na fibromialgia: um estudo piloto randomizado

### R E S U M O

#### Palavras-chave:

Fibromialgia  
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Avaliar os efeitos do treinamento aeróbico e do alongamento sobre os níveis séricos de serotonina (5-HT) e seu principal metabólito ácido 5-hidroxiindolacético (5-HIAA).

Foram randomizadas 22 mulheres com fibromialgia (FM) em uma de duas modalidades de exercício (exercício aeróbico de caminhada ou exercício de alongamento) a serem realizadas três vezes por semana, por 20 semanas. Os níveis séricos de 5-HT e 5-HIAA foram avaliados antes e após o programa de exercícios por cromatografia líquida de alta eficiência (CLAE) com detecção colorimétrica.

A análise de grupo (pré-pós) mostrou que os níveis séricos de 5-HT e 5-HIAA mudaram significativamente no grupo aeróbico durante o período de 20 semanas de terapia (5-HT:  $p = 0,03$ ; 5-HIAA:  $p = 0,003$ ). No grupo alongamento, contudo, não foi observada qualquer alteração estatisticamente significativa (5-HT:  $p = 0,491$ ; 5-HIAA:  $p = 0,549$ ). Comparações estatísticas das medidas de laboratório entre os grupos constataram que o treinamento aeróbico foi superior ao alongamento, aumentando significativamente os níveis de 5-HIAA (teste  $F - 6,61$ ;  $p = 0,01$ ); porém, a diferença média entre os grupos a respeito dos níveis de 5-HT não atendeu aos critérios de relevância (teste  $F = 3,42$ ;  $p = 0,08$ ).

O treinamento aeróbico aumenta os níveis de 5-HIAA e 5-HT e poderia explicar porque o exercício aeróbico pode melhorar os sintomas de pacientes com síndrome de fibromialgia mais que o exercício de alongamento.

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Physical exercise is a low-cost, safe, and efficient intervention for the treatment of the fibromyalgia syndrome (FM). There is evidence of its efficacy not only in the reduction of pain and the number of tender points, but also in the improvement of quality of life, mood, and other psychological aspects.<sup>1,2</sup>

It is believed that all types of physical exercise are beneficial, but the greatest evidence supports the benefits of aerobic training.<sup>2,3</sup> Although it has been established over the last two decades that exercise is fundamental for the treatment of FM, the mechanisms involved remain unknown.

Based on studies with animal models, with healthy humans, and in a variety of human diseases, it appears that exercise acts upon many sites of pain modulation, and therefore, may influence numerous pathophysiologic mechanisms. For example, aerobic exercise is known to increase peripheral levels of beta-endorphins,<sup>4,5</sup> to influence the serotonergic system,<sup>6</sup> to decrease sympathetic activity,<sup>7</sup> to improve sleep,<sup>8</sup> and to foster a sense of psychological well-being.<sup>9,10</sup>

Published clinical trials have demonstrated that aerobic conditioning is superior to stretching as an intervention to improve FM pain, functional capacity, and quality of life.<sup>1-3</sup> It was also observed that aerobic conditioning was efficient at improving emotional aspects of this disorder, while stretching offers no apparent clinical benefit.<sup>1</sup> One hypothesis to explain these results posits that aerobic exercise may increase the availability of biogenic amines such as serotonin and norepinephrine to improve anxiety/depression through their effects on neuroendocrinologic mechanisms.<sup>1,11</sup>

This study aimed to evaluate the effects of aerobic training and stretching on serum levels of serotonin (5HT) and its main metabolite, 5-hydroxyindolacetic acid (5HIAA).

Twenty-two sedentary women were sequentially selected according to the timing of their arrival to the rheumatology

outpatient clinic of the Universidade Federal de São Paulo. They were aged between 18 and 60 years and met the 1990 classification criteria of the American College of Rheumatology (ACR 1990).

All were randomized into one of two exercise modalities (aerobic walking exercise or stretching exercise) to be accomplished three times a week for 20 weeks. The randomization ratio was two patients in the aerobic exercise group for each person in the control group (2:1). Patients with any of the following were excluded: cardiorespiratory diseases which limited their physical activity, neurologic disorders, body mass index > 35, hypothyroidism, or any rheumatic disease. All patients were newly diagnosed and had never undergone any previous treatment for their FM symptoms. Only acetaminophen was allowed as rescue medication during the study. The study project was approved in the Ethics Committee of the Universidade Federal de São Paulo. All potential study participants were provided written information regarding each aspect of the study, and no study activity was undertaken with a subject before an informed consent was signed.

Study subjects were evaluated by a blinded investigator at the beginning and at the end of 20 weeks (end of the exercise program). Clinical benefits and improvement of their conditioning with the active intervention group were previously published.<sup>1</sup> Blood samples were drawn from an arm vein before exercise in the beginning and at the end of the study. The sera were stored at  $-70^{\circ}\text{C}$  until analyzed. The tubes containing the serum samples were number-coded in order to blind the laboratory personnel regarding treatment group and the sequence of sample collection. Analytical measurements of serum 5HT and 5-HIAA were accomplished by high performance liquid chromatography (HPLC) with colorimetric detection.

For the statistical analyses, the Statistical Package for the Social Sciences (SPSS), release 12.0, was used. Student's t-test and paired t-test were used to compare the average concentrations of the metabolites (5HT and 5HIAA) from each group (aerobic and stretching) before and after the intervention. Analysis of variance for repeated measures (ANOVA) was performed to compare the metabolite levels in both groups. Average differences were considered to be statistically significant when  $P < 0.05$ .

Table 1 shows that 14 of the 22 female study subjects were randomized to the aerobic exercise group and eight were randomized to the stretching group. There was no significant difference in demographics between the study groups at baseline when considering age, body mass index, pain visual analog scale (VAS), and quality of life.

All subjects completed the 20-week program, but two patients from the stretching group were excluded since not enough serum to perform HPLC analyses was obtained.

At baseline, there was no statistically significant difference in the values between groups for 5HT ( $P = 0.71$ ), but the initial 5HIAA values were significantly higher in the stretching exercise group ( $P = 0.009$ , Table 1).

Intra-group analysis (pre/post) demonstrated that serum levels of both 5HT and 5HIAA changed significantly in the aerobic group during the 20-week course of therapy (Table 1). In the stretching group, however, no statistically significant change was observed (Table 1).

Inter-group statistical comparisons of laboratory measures demonstrated that aerobic training was superior to stretching in that it significantly increased the levels of 5HIAA (F test = 6.61;  $P = 0.01$ ), but the average difference between groups on the levels of 5HT was not statistically significant (F test = 3.42;  $P = 0.08$ ). Despite the initial difference in 5HIAA values, the ANOVA test showed significance considering the change pre/post between groups.

Although physical exercise is widely acknowledged as indispensable for the treatment of FM, there are very few studies that have explored the mechanisms responsible for the achieved benefits. In healthy subjects, it is known that aerobic physical activity is capable of increasing peripheral levels of  $\beta$ -endorphins,<sup>4</sup> promoting a decrease in sympathetic activity,<sup>7</sup> improving sleep,<sup>7</sup> and facilitating psychological stability.<sup>8,9</sup> Regarding the monoamine-serotonergic system, physical exercise can increase the sensitivity of certain types of 5HT receptors,<sup>12</sup> and is also capable of increasing central<sup>6,13</sup> and

serum levels of 5HT. It is believed that running may elevate central nervous system levels of 5HT through lipolysis and subsequent release of free fatty acids, which dislocate tryptophan from serum albumin, resulting in greater availability of free tryptophan for 5HT synthesis.<sup>13</sup> In addition, exercise increases total platelet volume and 5HT concentration in platelets, resulting in elevation of total 5HT blood levels.

It is known that serum 5HT levels are decreased in FM,<sup>14</sup> and that low levels of 5HT have been implicated in many aspects of FM pathophysiology, including imbalance of the hypothalamic pituitary axis, and autonomic dysfunction that leads to sympathetic hyperactivity and contributes to sleep disorders, anxiety, Raynaud's phenomenon, and sicca symptoms.<sup>15,16</sup> The effectiveness of the available pharmacologic agents that increase serotonin levels in FM supports the concept that this neurotransmitter is important to the pathogenesis of FM.<sup>17</sup>

One of the mechanisms that contribute to the chronic widespread allodynia in FM is the increased pronociception and decreased descending inhibition or antinociception.<sup>18,19</sup> Serotonin is one of the neurochemicals involved in the antinociception; since it is diminished in FM patients, it contributes to the chronic allodynia.<sup>14,19</sup>

The effects of physical exercise on 5HT levels in patients with FM have not been previously studied. However, it was demonstrated in patients with chronic lumbar pain that spinal stabilization exercises produce an increase in serum 5HT levels, which could help to explain the positive results of this type of exercise in the management of chronic back pain.<sup>20</sup>

The present results demonstrated that the statistically significant changes in serum levels of 5HT and 5HIAA, which occurred during the course of the study, could be attributed to aerobic exercises but not to stretching exercises. Aerobic training was superior to stretching in its ability to elevate 5HIAA levels. The aerobic conditioning also showed improvement in emotional and psychological aspects of the disorder, whereas stretching did not. In the same study subjects, FM pain was more responsive to aerobic activity than to stretching.<sup>1</sup> Therefore, it appears that the serotonergic system may be an important modulator of the neuroendocrinological mechanisms through which aerobic exercise can improve pain, anxiety, and depression in FM.

It should be emphasized, however, that stretching cannot be considered a placebo intervention, since the present results demonstrated that this kind of exercise had some impact on FM pain.<sup>1</sup> It is possible that stretching exercise has mechanical benefits through its effects on comorbid conditions such as myofascial pain syndrome, which can coexist with FM in a substantial number of patients.<sup>21</sup> Even mild stretching exercise could mobilize fascial tissue,<sup>22,23</sup> which may prove to be more important than currently perceived. Additional studies are needed to test these hypotheses.

When aerobic training was statistically compared with stretching, it was superior with regard to raising serum 5HIAA levels, but did not meet statistical difference for serum 5HT levels. It is possible that a larger sample size would show significance. Serum levels of biogenic amines can vary with fasting, food ingestion, medications, alcohol ingestion, use of illegal drugs, hormones, and many stressful conditions.<sup>24</sup> In addition, serum 5HT levels are physiologically regulated, so

**Table 1 – Baseline demographic and clinical measures from fibromyalgia syndrome patient participants.**

Variable	Stretching exercise group	Aerobic exercise group	Inter-group statistic
Mean age [years]	47 ± 10	44 ± 11	$P = 0.335$
BMI [kg/m]	26 ± 3	28 ± 6	$P = 0.186$
Pain VAS [cm/10]	6.19 ± 1.64	6 ± 2.1	$P = 0.325$
FIQ	5.30 ± 1.50	4.89 ± 1.65	$P = 0.303$

VAS, visual analog scale; BMI, body mass index; FIQ, fibromyalgia impact questionnaire.

an increase in 5HT production might logically be expressed as an increase in the concentration of its stable metabolite.

This was a pilot study, limited mainly by the small sample size. Despite the randomization of patients included in the analysis, the small sample size could explain the significant difference in 5HIAA between patients before exercise training. In addition, the level of the study subjects' leisure activity was not evaluated and could have influenced the results. The serum analyses were carried out four years after collection of the blood; despite cold/dark storage, sample stability could be a bias. It is known, however, that both 5HT and 5HIAA are stable if kept frozen and protected from light.<sup>25</sup>

Other studies are necessary to fully understand the impact of physical exercise on central and serum levels of other chemical mediators, on the functioning of the autonomic nervous system, on the neuroendocrine production of the HPA axis, and on the brain's gray matter.

### Conflicts of interest

The authors declare no conflicts of interest.

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