**Evolution of pain and central sensitization in patients with fibromyalgia after a specific work of Pilates or stretching.**

ACRONIMO:EDSEFIBRO

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1. INTRODUCTION.

Fibromyalgia (FM) is one of the rheumatic diseases that occurs in Spain with a prevalence of 2.4%. This is associated, according to the study of EPISER (2016), to a worse quality of life, requiring, in addition, a high consumption of health and social resources (1), as a consequence, it constitutes a common and debilitating chronic health problem.

The gender difference is 4.2% for women, compared to 0.2 for men (2). This disease is characterized by the presence of generalized pain, fatigue, sleep disorders (short duration, low quality and efficiency), presence of "tender points", and a multitude of other symptoms that accompany the main symptomatology (3,4).

Due to the large number of conditions suffered by these patients, a study is necessary to assess how pain affects and if there is a relationship with respect to the central sensitization in them.

Pain, in FM, follows the central physiopathological mechanisms. This leads to the hypothesis that the central nervous system (CNS) is hyperexcitable in these patients, and that the temporary sum is more facilitated, unlike the inhibitory modulation, which is impaired (5).

Pain is a complex perception that is influenced by previous experience and by the context within which the noxious stimulus occurs. "Nociception" is the physiological response to tissue damage or previous tissue damage (6). The definition is supported by the International Association for the Study of Pain, and is described as: "Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or is described in terms of such damage" (7).

Hyperalgesia, a concept that "surrounds" the definition of fibromyalgia, can be explained by an increase in the pain sensitivity of nociceptors located in deep tissue (peripheral sensitization) or by an increase in the responses of the dorsal horn neurons ( central sensitization) (6,8).

The dissemination of pain and sensitivity is related to the increase in synaptic activity in central neurons and to changes in the downward control of supraspinal centers. The manifestations related to aspects of sensitization can be assessed quantitatively through sensory tests, such as pressure algometry (quantitative palpation) and sleeve algometry (8). The repeated pressure stimulation can evaluate the degree of temporary addition, which is a marker of the level of central sensitization, since the area of ​​referred muscular pain is extended. The transition from localized acute musculoskeletal pain to generalized chronic pain is related to the progression of central and peripheral sensitization. This sensitization for the chronification of pain should be evaluated by means of suitable biomarkers for pain. However, not all nociceptive signals are perceived as pain and vice versa. Not every pain sensation originates from nociception (6, 8).

New research is underway to find out if there are differences between pain processing in healthy subjects compared to fibromyalgia patients. These investigations provide us with the description of different areas in the central nervous system that are altered, not only functionally, but also structurally in these patients. "It seems that these involved areas extend beyond the pain circuits, which may explain the great variety of symptoms found in patients with fibromyalgia" (9).

However, knowledge about the physiological mechanism of central sensitization, pathophysiology and pain processing in fibromyalgia is not enough to know what would be the best treatments to address this problem. This study aims to let us know a little more closely, what happens with the sensitization processes

central when patients receive one type or another of intervention, in order to approach the development of treatments that improve the quality of life.

2.- CONCEPTUAL HYPOTHESIS.

A program of Pilates exercises will significantly improve symptoms in patients with fibromyalgia, generating a decrease in pain, improving sleep quality, improving the impact of the disease, improving the quality of life, improving the impact in optimism compared to a stretching program.

3.- OBJECTIVES.

3.1. Main goal

To determine the modification of pain in patients with fibromyalgia after 4 months of guided exercise.

**3.2. Secondary objectives.**

• Define how a Pilates and stretching program interferes with sleep quality for 4 months in a patient with fibromyalgia.

• Verify if a program of Pilates and stretching for 4 months, produces changes in the quality of life in patients with fibromyalgia.

• Check if a Pilates training and stretching done during 4 months produces changes in the impact of fibromyalgia in patients who suffer from it.

• Verify if there are changes in optimism in patients with fibromyalgia after carrying out a program of Pilates and stretching.

**4.- MATERIAL AND METHODS.**

**4.1. Study design.**

Study of clinical trial type, randomized, double blind.

**4.2 Subjects and scope of the study**.

The study population will be taken from patients who belong to the association of Fibromyalgia "Afinsyfacro" and who meet the inclusion and exclusion criteria proposed in this study.

**4.2.1 Inclusion criteria.**

• Adults diagnosed with Fibromyalgia according to the latest revision of criteria of the American College of Rheumatology (ACR) (10).

• Pain with a minimum duration of 3 months (10,11).

• Able to read and understand the Spanish language.

• Men and women between the ages of 18 and 65 (12).

4.2.2 Exclusion criteria.

• Present recent musculoskeletal injuries (less than 3 weeks).

• Not have other diseases that represent a contraindication for the performance of therapeutic exercise.

• Suffering from orthopedic, neurological, or cardiovascular comorbidities (13) that prevent the development of a specific exercise program.

**4.2.3 Sample size.**

The representative sample of the population will be of 74 male and female patients with fibromyalgia belonging to the association Afinsyfacro de Móstoles. The sample size is calculated with a program of the Clinical and biostatistical epidemiology unit of the University Hospital Complex of A Coruña. A sample size of 63 subjects is estimated, considering the finding of 2 points of difference in the clinically relevant NRS. For the calculation, a confidence level of 95% was established, with a power of 99%. In addition, the sample size is adjusted to 15% of the proportion of losses, resulting in a sample adjusted to the losses of 74 subjects.

**4.3 Sampling.**

A non-probabilistic sampling will be carried out for convenience of the association of Fibromyalgia "Afinsyfacro".

**4.4 Recruitment and recruitment.**

The recruitment will be carried out voluntarily by patients with fibromyalgia, only those who meet the proposed inclusion and exclusion criteria will be included. Beforehand, the information sheet of the study will be provided (Annex I) and the informed consent will be signed (Annex II) of any person wishing to be part of this study.

**4.5 Randomization, blinding and allocation**

Randomisation will be carried out through a computerized randomisation system (randomized.com) that guarantees concealment of the allocation, resulting in 30 subjects per intervention group. An external co-worker will sequence the participants in the study. The subjects and evaluators who will collect or analyze the data will not know the objectives of the study and the treatment allocation group, to guarantee the blinding of the participants and the blinding of the outcome assessor, respectively. The clinician in charge of the intervention will not participate in the evaluation protocol and will not know what the objectives of the study were.

**4.6. Procedure for obtaining data.**

An information sheet (Annex I) will be provided with an explanation of the objective and content of the study for the recruitment of the participants. When patients agree to participate and meet the inclusion and exclusion criteria, they will sign an informed consent (Annex II) before the start of the first treatment session. Patients who do not wish to participate will be counted and the reasons will be noted.

A member of the research team will be responsible for both interventions, 30-minute sessions held twice a week for 4 months, with a maximum of 10-12 participants per group. All sessions will be carried out under the same environmental conditions.

Sociodemographic variables, physical measurements, comorbolidade.

**4.8 Intervention**

Participants will complete a program of Pilates or stretching sessions taught by a physiotherapist and licensed in Physical Activity and Sports. The program will consist of 30 minute sessions held twice a week for 4 months.

**4.8.1 Pilates Group**

Exercise sessions varied month by month. In the first month, the sessions will begin with six repetitions of each exercise and 40 seconds of rest between sets. In the following months, the number of repetitions will increase up to ten repetitions of each exercise with only 15 seconds of rest between sets of exercises. An attendance record will be maintained. The exercise program will follow the basic principles of the Pilates method with a special emphasis on movements from low to intermediate level of difficulty to adapt them to the physical capacity of the patients. The protocol includes several modules, which will be similar to those described by Altan: basic principles, breathing exercises, posture exercises, neutral position search, sitting exercises, analgesic exercises, stretching exercises and proprioceptivity exercises.

**4.8.2 Group of stretches**

Same stretching program for four months at a rate of two days per week and with a duration of 30 minutes per session. Included in this program are stretches of choice for their role in global postural reeducation. Paravertebral, gluteus, hamstrings, hip adductors, latissimus dorsi, pectoral and a final stretch that includes the paravertebrals, gluteus, ischiotibial and triceps surae are included. The protocol, defined by Assumpcäo A, is as follows: 1-4th week, 3 repetitions will be performed, in the 5th week, 4 repetitions for each muscle group; in the 6th week onwards, 5 repetitions (29) will be performed.

**5.- ETHICAL-LEGAL ASPECTS.**

This study will be carried out following the foundations of research ethics in the Belmont report (Ethical principles and guidelines for the protection of human subjects of research, 1979), the ethical requirements contained in the Declaration of Helsinki on Ethical Principles for Research Doctors in Human Beings (2008), the International Ethical Guidelines for Biomedical Research with Humans of the Council of the European Agency for International Organizations of Medical Sciences (Geneva, 2002) and the Convention for the Protection of Human Rights and Dignity of the human being with respect to the applications of biology and medicine in the European Union (Declaration of Oviedo, 1997).

At all times the highest professional conduct and absolute confidentiality will be maintained according to the Data Protection Law (Organic Law 15/1999, of December 13, "Protection of Personal Data" published in BOE nº298, de14 de December) and Law 41/2002, of November 14, basic regulatory of the autonomy of the patient and of rights and obligations in matters of information and clinical documentation (BOE nº274, of November 15). The R.D. 1720/2007 approving the development of the LOPD.

Finally, when completing the questionnaires in an online platform, the appropriate professional conduct will be maintained and compliance with confidentiality will be maintained according to the Data Protection Law (Organic Law 3/2018, of December 5, 2018, with reference BOE-A -2018-16673 with nº 294, pages 119788 to 119857) of protection of data of "Personal Character" and guarantee of digital rights.

**6.- STATISTICAL ANALYSIS.**

The statistical analysis will be performed using SPSS 22.0 software (SPSS Science, Chicago, United States). Descriptive statistics will be represented in tables as mean, standard deviation and 95% CI for continuous measurements or percentages for categorical answers. We will examine the normality with the Shapiro-Wilk test of the outcome variables. The two-sample t test or the X2 test will be used to examine possible differences in reference values ​​and demographic variables between the two groups; or we will apply the U Mann Whitney test when they do not fulfill normality. The variance analysis model with mixed linear effects will be used to test the profile of the change in the outcome variable at the beginning of the study, after the intervention and follow-up (at 15 days, one month, two months, three months and four months after, and after 6 months of follow-up) (the Bonferroni correction was used for the post hoc analysis). The intra-group comparison between changes in different evaluations will be analyzed with post hoc analysis. The overall clinical effects for the analysis of repeated measures were calculated by the Eta square value, where the effect of 0.01 was considered small, 0.06 was considered median and 0.14 was considered large. The statistical analysis will be carried out considering

**8.-** **Bibliography .**

1. Seoane-mato D, Sánchez-piedra C, Silva-fernández L, Sivera F, Blanco FJ, Pérez F, et al. Prevalence of rheumatic diseases in adult population in Spain (EPISER 2016 study): Aims and methodology. Reumatol Clin. 2019;15(2):90-96.

2. Lee JY, Guy, Stacey GD, Lukacs MJ, Letwin ZA, Fakhereddin MF, Al-Narsi IJ, et al. Management of fibromyalgia syndrome Cognitive-behavioral therapy (CBT) for healthcare professionals. UWOMJ. 2019; 87(1):34-7

3. Gota CE. What you can do for your fibromyalgia patient. Cleve Clin J Med. 2018 ;85(5):367 -76.

4. Wu YL, Chang LY, Lee HC, Fang SC, Tsai PS. Sleep disturbances in fibromyalgia. A meta analysis of case-control studies. Journal of Psychosomatic Research. 2017;96:89-97.

5. Meeus M, Nijs J. Central sensitization: a biopsychosocial explanation for chronic widespread pain in patients with fibromyalgia and chronic fatigue syndrome. Clin Rheumatol. 2007;26(4):465-73.

6. Winkelstein BA. Mechanisms of central sensitization, neuroimmunology & injury biomechanics in persistent pain: Implications for musculoskeletal disorders. Journal of Electromyography and Kinesiology.2004;14(1):87-93

7. Merskey H, Bogduk N. Classification of Chronic Pain: Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms. Pain Suppl. 1986;3:S1-226

8. Staud R, Cannon RC, Mauderli AP, Robinson ME, Price DD, Vierck CJ. Temporal summation of pain from mechanical stimulation of muscle tissue in normal controls and subjects with fibromyalgia syndrome. Pain. 2003;102(1-2):87-95.

9. Gomez-Arguelles JM, Maestu-Unturbe C, Gomez-Aguilera EJ. [Neuroimaging in fibromyalgia]. Rev Neurol. 2018;67(10):394–402.

10. Wolfe F. New American College of Rheumatology criteria for fibromyalgia: a twenty-year journey. Arthritis care & research. United States. 2010;62(5):583-4.

11. Casanueva B. Tratado de fibromialgia. 1ª Edición. Santander: Cantabria Imagen; 2007.

12. Ericsson A, Palstam A, Larsson A, Löfgren M, Bileviciute-Ljungar I, Bjersing J, et al. Resistance exercise improves physical fatigue in women with fibromyalgia: A randomized controlled trial. Arthritis Res Ther. 2016; Arthritis Res Ther. 2016;18:176

13. Larsson A, Palstam A, Löfgren M, Ernberg M, Bjersing J, Bileviciute-Ljungar I, et al. Resistance exercise improves muscle strength, health status and pain intensity in fibromyalgia-a randomized controlled trial. Arthritis Res Ther. 2015;17:161-76

14. Marques AP, Ferreira EAG, Matsutani LA, Pereira CAB, Assumpção A. Quantifying pain threshold and quality of life of fibromyalgia patients. Clin Rheumatol. 2005;24(3):266-71.

15. Koo TK, Guo JY, Brown CM. Test-retest reliability, repeatability, and sensitivity of an automated deformation-controlled indentation on pressure pain threshold measurement. J Manipulative Physiol Ther. 2013;36(2):84–90.

16. Hogeweg JA, Langereis MJ, Bernards AT, Faber JA, Helders PJ. Algometry. Measuring pain threshold, method and characteristics in healthy subjects. Scand J Rehabil Med. 1992;24(2):99–103.

17. Walton D, MacDermid J, Nielson W, Teasell R, Chiasson M, Brown L. Reliability, Standard Error, and Minimum Detectable Change of Clinical Pressure Pain Threshold Testing in People With and Without Acute Neck Pain. Orthop Sports Phys Ther. 2011;41(9):644-50.

18. Arendt-Nielsen L, Graven-Nielsen T. Central sensitization in fibromyalgia and other musculoskeletal disorders. Curr Pain Headache Rep. 2003;7(5):355–61.

19. Cagnie B, Coppieters I, Denecker S, Six J, Danneels L, Meeus M. Central sensitization in fibromyalgia? A systematic review on structural and functional brain MRI. Arthritis Rheum 2014;44(1):68–75.

20. Gracely RH, Grant MAB, Giesecke T. Evoked pain measures in fibromyalgia. Best Pract Res Clin Rheumatol. 2003;17(4):593-609.

21. Potvin S, Paul-Savoie E, Morin M, Bourgault P, Marchand S. Temporal summation of pain is not amplified in a large proportion of fibromyalgia patients. Pain Res Treat. 2012; 2012: 938595.

22. Scerbo T, Colasurdo J, Dunn S, Unger J, Nijs J, Cook C. Measurement Properties of the Central Sensitization Inventory: A Systematic Review. Pain Pract. 2018;18(4):544-554.

23. Graven-Nielsen, Arendt-Nielsen L. Assessment of mechanisms in localized and widespread musculoskeletal pain. Nat Rev Rheumatol. 2010 Oct;6(10):599-606.

24. Neblett R, Cohen H, Choi Y, Hartzell MM, Williams M, Mayer TG, et al. The Central Sensitization Inventory (CSI): establishing clinically significant values for identifying central sensitivity syndromes in an outpatient chronic pain sample. J Pain. 2013 M;14(5):438–45.

25. Ferreira-Valente MA, Pais-Ribeiro JL, Jensen MP. Validity of four pain intensity rating scales. Pain. 2011;152(10):2399–404.

26. Kennedy DL, Kemp HI, Ridout D, Yarnitsky D, Rice ASC. Reliability of conditioned pain modulation: a systematic review. Pain. 2016;157(11):2410–9

27. Perczek R, Carver CS, Price AA, Pozo-Kaderman C. Coping, mood, and aspects of personality in Spanish translation and evidence of convergence with English versions. J Pers Assess. 2000;74(1):63-87

28. Hernández RL, González Ramírez MT. Propiedades psicométricas de la versión española del test de optimismo revisado (lot-r) en una muestra de personas con fibromialgia. Ansiedad y Estres. 2009; 35(2):58-67

29. Macías Fernández JA, Royuela A. La versión española del Índice de Calidad de Sueño de Pittsburgh. Informaciones Psiquiatricas. 1996; (146):465-72.

30. Assumpcao A, Matsutani LA, Yuan SL, Santo AS, Sauer J, Mango P, et al. Muscle stretching exercises and resistance training in fibromyalgia: which is better? A three-arm randomized controlled trial. Eur J Phys Rehabil Med.2018;54(5):663–70.