

Fibromyalgia

Subjects: Others

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Fibromyalgia (FM) is a complex multifactorial syndrome characterized by chronic widespread pain that is often accompanied by fatigue, cognitive problems and sleep disturbances causing a considerable decline in patient quality of life.

Keywords: fibromyalgia ; chronic pain ; cortisol ; treatment ; meta-analysis

1. Introduction

Fibromyalgia (FM) is a complex multifactorial syndrome characterized by chronic widespread pain that is often accompanied by fatigue, cognitive problems and sleep disturbances causing a considerable decline in patient quality of life [1][2][3]. Over the past decades, several criteria have been defined for the classification, diagnosis and detection of FM, but criteria reflecting the present understanding of this disease that could help clinicians and researchers are lacking. This lack is clinically relevant during the clinical practice since criteria have to be valid, reliable and consistent to identify, assess and classify patients with FM and to make the most accurate treatment decision. According to research criteria, patients are required to have pain in the axial skeleton, above and below the waist and on both sides of the body. With the goal of a multifaceted diagnosis, in 2013, a working group on fibromyalgia was created to assess new diagnostic approaches to help identify FM in clinical practice. This diagnostic taxonomy (ACTION-APS Pain Taxonomy, AAPT) classifies chronic pain according to the dimensions: (1) core diagnostic criteria, (2) common features, (3) common medical comorbidities, (4) neurobiological, psychosocial and functional consequences, and (5) putative neurobiological and psychosocial mechanisms, risk factors, and protective factors [4][5].

Current research efforts suggest that the underlying basis of the symptoms of FM could be the altered physiology of the central nervous system, whereby the abnormal processing of pain signals plays an important role in its pathogenesis. This nociceptive system dysregulation may arise from a combination of interactions among the autonomic nervous system, neurotransmitters, cytokines and hormones, among others [6].

Cortisol is an essential steroid hormone produced in the suprarenal cortex within the suprarenal gland [7][8][9]. Levels of cortisol both in blood and saliva vary throughout the day, reaching their peak approximately at 8 am and showing lowest levels between 12 pm and 4 am, or 3 to 5 h after the onset of sleep [8]. Cortisol concentrations are related to stress levels and blood glucose concentrations.

The hypothalamic–pituitary–adrenal axis (HPA) is considered a mediator of cortisol production. HPA activation has been associated with the severity of chronic musculoskeletal pain [7][10][11][12] and with fluctuations in perceived pain [13]. However, when analyzing the effects of cortisol on chronic pain, clinical studies have detected their inverse relationship. Thus, some investigations have shown that a higher cortisol concentration is related to a lower pain intensity [14][15], and accordingly, lower cortisol concentrations have been linked to greater levels of pain [7][16]. Pain symptoms are among the five main reasons patients with FM visit the emergency room [17].

Several explanations have been put forward for the low cortisol reactivity observed in patients with FM. For example, a possible reason for HPA hypofunction in FM would be the low secretion of corticotropin releasing hormone (CRH) by the hypothalamus and secondary atrophy of the suprarenal glands due to this low chronic stimulation because of reduced adrenocorticotrophic hormone (ACTH) levels [18]. In contrast, it has been also proposed that the cause could be a reduced response of suprarenal cortisol to ACTH. Hence, diminished adrenocortical sensitivity to ACTH could be attributed to the complete regulation of suprarenal receptors, but genetic variation and morphological changes in the suprarenal gland along with atrophy or diminished volume could also contribute [19][20].

Due to the need for more evidence when trying to understand the relationship existing between cortisol concentrations and chronic widespread pain, this systematic review and meta-analysis sought to analyze and summarize the latest literature examining this topic in patients with FM. Main goals were: (a) to identify studies conducted in the past 10 years

analyzing variations in cortisol levels and perceived pain produced in response to a treatment intervention or between subjects with and without FM; (b) to assess the methodological quality of the studies identified; (c) to calculate the effect sizes of the interventions proposed on cortisol and pain; and (d) compare the effectiveness of the interventions.

2. Possible Relationship between Cortisol Levels and the Pain Symptoms of Fibromyalgia

The results indicate some individual effects of therapeutic interventions on both cortisol levels and several measures of pain though overall effect sizes were insignificant.

Fibromyalgia affects the 2.1% of the world population and 2.4% of persons in Spain. It is diagnosed mainly in women, the reported ratio women:men varying from 2:1 ^[21] or 3:1 ^[22] to 10:1 ^{[20][23][24]}. This much larger proportion of affected women is well reflected in this review in which all study participants were women. In effect, it is difficult to find studies including both sexes and those that have done so have examined a smaller proportion of men ^{[25][26]}.

The best therapeutic approach to fibromyalgia is integrating pharmacological and non-pharmacological treatments (exercise therapy, patient education and cognitive behavioral therapy) while actively involving patients in their own care process. In particular, the important role of stress reduction, sleep and physical exercise as basic self-management strategies should be stressed ^[1]. Pharmacological agents include analgesics, antidepressants, anticonvulsants and muscle relaxants ^[2]. Only one of the studies analyzed the impact of pharmacological therapy (low dose dexamethasone) in patients with FM. In response to the drug, cortisol levels were found to increase following measurement of the pressure pain threshold, and post hoc analysis of measures revealed a parallel increase in levels of pain. Individualized treatments prescribed by multidisciplinary teams including clinicians with expertise in patient education and mental health, physical or occupational therapists offer improved outcomes over pharmacological treatments alone ^[1].

The treatment interventions tested in the studies reviewed were often exercise related ^{[18][27][28]}. However, the therapeutic value of these exercise interventions for FM emerged as low. This may be mainly attributed to incomplete descriptions of the exercise programs tested and poor patient adherence ^[29]. Physical therapy was the second most common intervention tested ^{[30][31]} and one study was based on lifestyle interventions ^[32]. Three of the studies involved an observational assessment ^{[33][34][35]}. The reports selected for this review were required to fulfil strict inclusion criteria related to pain and cortisol and thus do not really reflect usual treatment interventions. According to Basavakumar et al., treatments most often used for FM are interventions on lifestyle, followed by medication and non-pharmacological treatments, such as physical therapy and physical exercise, along with the use of nutrition supplements ^[36].

In the studies selected, cortisol levels were determined using diagnostic tests on blood, saliva or urine samples. Several authors have established that morning cortisol levels in serum ^[37], saliva ^{[38][39]} or hair ^[39] are lower in subjects with chronic musculoskeletal pain ^[40], FM ^{[37][38]} or chronic fatigue syndrome ^[37].

Several independent studies for this review were selected according to descriptive statistics and effect sizes reported for the effects of several predictive variables on cortisol levels. In two of these studies, significant medium size effects were observed ^{[33][35]}, while in three, effects were both significant and large ^{[18][32][28]}.

In a meta-analysis, Tak et al. compared 85 cases of FM and controls. These authors detected a significant reduction in baseline cortisol in all female patients with FM compared to healthy control subjects and described a participating role of HPA in functional somatic disorders including fibromyalgia ^[41]. Low baseline cortisol levels in FM patients were also reported in the articles reviewed here ^{[18][30][31][28]}.

There is evidence of disassociation between total and free cortisol levels in patients with FM, who generally show normal free cortisol levels in plasma and saliva despite total cortisol levels being diminished ^[6]. Other authors have observed that salivary daily cortisol levels are reduced while cumulative cortisol levels in hair remain normal ^[42]. A comparison between FM patients with neck and shoulder pain and healthy controls revealed significantly lower awakening cortisol levels in the patients ^[43]. The disparate results obtained in the different studies reviewed are consistent with findings in the literature.

Analysis of pain in the different studies has revealed poor agreement between the high therapeutic value of exercise and adherence to exercise recommendations.

The results of the studies selected indicated large significant effects of several interventions on the pain tolerance threshold and pressure pain threshold ^{[18][33][44][34][35][28]}.

In general, the effects observed were variable. This variability could be explained by the heterogeneity of both interventions and study designs. Cortisol measurement protocols (in urine or blood) and pain tolerance or threshold tests were conducted using different instruments and protocols. This disparity might explain why Torgrimson-Ojerio et al. [28] noted significant reductions in cortisol in their FM group while others report significant reductions in the control group [32]. Variation in pain was described in the study by Geiss et al., who used the pressure pain threshold method [44], while Pernambuco et al., Riva et al., and Stehlik et al., measured pain more subjectively through the fibromyalgia impact questionnaire (FIQ) and visual analogue scale (VAS), respectively [32][34][35]. While this variability suggests these data should be analyzed with caution, they seem to indicate that a guided combined physical therapy/aerobic exercise program involving sessions two days a week over 5 weeks could help relieve pain and reduce plasma cortisol levels [18][30]. Long-term experimental studies based on multifaceted programs could help standardize interventions and detect larger more consistent pain alleviating effects of exercise.

In response to a treatment intervention such as those described in the studies reviewed here, patients with FM show improved pain tolerance and perceived pain thresholds and these improvements are largely reflected by a better perceived health state [4]. However, although the results of the studies examined here and those of most studies in the literature are promising, sample sizes have been small. Thus, larger therapeutic interventions are needed to support the evidence available before their generalized implementation. While fibromyalgia is much better understood and managed today than before, more work is needed on non-pharmacological approaches to symptom treatment to further improve patient quality of life.

References

1. Laroche, F. Fibromialgia. *EMC Apar. Locomot.* 2014, 47, 1–9.
2. Sifuentes-Giraldo, W.; Morell-Hita, J. Fibromialgia. *Med. Programa Form. Médica Contin. Acreditado* 2017, 12, 1586–1595.
3. Aman, M.M.; Yong, R.J.; Kaye, A.D.; Urman, R.D. Evidence-Based Non-Pharmacological Therapies for Fibromyalgia. *Curr. Pain Headache Rep.* 2018, 22, 33.
4. Arnold, L.M.; Bennett, R.M.; Crofford, L.J.; Dean, L.E.; Clauw, D.J.; Goldenberg, D.L.; Fitzcharles, M.-A.; Paiva, E.S.; Staud, R.; Sarzi-Puttini, P.; et al. AAPT Diagnostic Criteria for Fibromyalgia. *J. Pain* 2019, 20, 611–628.
5. Fillingim, R.B.; Bruehl, S.; Dworkin, R.H.; Dworkin, S.F.; Loeser, J.D.; Turk, D.C.; Widerstrom-Noga, E.; Arnold, L.; Bennett, R.; Edwards, R.R.; et al. The ACTION-American Pain Society Pain Taxonomy (AAPT): An Evidence-Based and Multidimensional Approach to Classifying Chronic Pain Conditions. *J. Pain* 2014, 15, 241–249.
6. Kaltsas, G.; Tsvieriotis, K. Fibromyalgia. In *Endotext* [Internet]; MDText.com, Inc.: South Dartmouth, MA, USA, 2020. Available online: <https://www.ncbi.nlm.nih.gov/sites/books/NBK279092/> (accessed on 28 October 2019).
7. Goodin, B.R.; Smith, M.T.; Quinn, N.B.; King, C.D.; McGuire, L. Poor sleep quality and exaggerated salivary cortisol reactivity to the cold pressor task predict greater acute pain severity in a non-clinical sample. *Biol. Psychol.* 2012, 91, 36–41.
8. Raff, H. Utility of Salivary Cortisol Measurements in Cushing's Syndrome and Adrenal Insufficiency. *J. Clin. Endocrinol. Metab.* 2009, 94, 3647–3655.
9. Chan, S.; Debono, M. Review: Replication of cortisol circadian rhythm: New advances in hydrocortisone replacement therapy. *Ther. Adv. Endocrinol. Metab.* 2010, 1, 129–138.
10. McBeth, J.; Chiu, Y.H.; Silman, A.J.; Ray, D.W.; Morriss, R.; Dickens, C.; Gupta, A.; Macfarlane, G.J. Hypothalamic-pituitary-adrenal stress axis function and the relationship with chronic widespread pain and its antecedents. *Arthritis Res. Ther.* 2005, 7, R992–R1000.
11. Neeck, G.; Reidel, W. Hormonal perturbations in fibromyalgia syndrome. *Ann. N. Y. Acad. Sci.* 1999, 879, 325–338.
12. Úbeda-D'Ocasar, E. Mejora en la Calidad de Vida y Disminución del Dolor en Pacientes con Fibromialgia Tratadas Mediante Terapia Manual EUD. *Cuest. Fisioter.* 2014, 43, 183–195. Available online: <http://www.cuestionesdefisioterapia.com/index.php/es/main/articulos/article/43/3/3> (accessed on 28 October 2019).
13. Fischer, S.; Doerr, J.M.; Strahler, J.; Mewes, R.; Thieme, K.; Nater, U.M. Stress exacerbates pain in the everyday lives of women with fibromyalgia syndrome—The role of cortisol and alpha-amylase. *Psychoneuroendocrinology* 2016, 63, 68–77.
14. Carnes, D.; Parsons, S.; Ashby, D.; Breen, A.; Foster, N.E.; Pincus, T.; Vogel, S.; Underwood, M. Chronic musculoskeletal pain rarely presents in a single body site: Results from a UK population study. *Rheumatology* 2007,

15. Al'Absi, M.; Petersen, K.L.; Wittmers, L.E. Adrenocortical and hemodynamic predictors of pain perception in men and women. *Pain* 2002, 96, 197–204.
16. Geiss, A.; Varadi, E.; Steinbach, K.; Bauer, H.W.; Anton, F. Psychoneuroimmunological correlates of persisting sciatic pain in patients who underwent discectomy. *Neurosci. Lett.* 1997, 237, 65–68.
17. Penney, L.S.; Ritenbaugh, C.; Elder, C.; Schneider, J.; Deyo, R.A.; DeBar, L.L. Primary care physicians, acupuncture and chiropractic clinicians, and chronic pain patients: A qualitative analysis of communication and care coordination patterns. *BMC Complement. Altern. Med.* 2015, 16, 30.
18. Genc, A.; Tur, B.S.; Aytur, Y.K.; Öztuna, D.; Erdoğan, M.F. Does aerobic exercise affect the hypothalamic-pituitary-adrenal hormonal response in patients with fibromyalgia syndrome? *J. Phys. Ther. Sci.* 2015, 27, 2225–2231.
19. Li, X.; Hu, L. The Role of Stress Regulation on Neural Plasticity in Pain Chronification. *Neural Plast.* 2016, 2016, 1–9.
20. Galvez-Sánchez, C.M.; Duschek, S.; Del Paso, G.A.R. Psychological impact of fibromyalgia: Current perspectives. *Psychol. Res. Behav. Manag.* 2019, 12, 117–127.
21. D'Agnelli, S.; Arendt-Nielsen, L.; Gerra, M.C.; Zatorri, K.; Boggiani, L.; Baciarello, M.; Bignami, E. Fibromyalgia: Genetics and epigenetics insights may provide the basis for the development of diagnostic biomarkers. *Mol. Pain* 2018, 15.
22. Sosa-Reina, M.D.; Nunez-Nagy, S.; Gallego-Izquierdo, T.; Pecos-Martín, D.; Monserrat, J.; Álvarez-Mon, M. Effectiveness of Therapeutic Exercise in Fibromyalgia Syndrome: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. *BioMed Res. Int.* 2017, 2017, 2356346.
23. Cabo-Meseguer, A.; Cerdá-Olmedo, G.; Trillo-Mata, J.L. Fibromyalgia: Prevalence, epidemiologic profiles and economic costs. *Med. Clín.* 2017, 149, 441–448.
24. Arout, C.A.; Sofuoglu, M.; Bastian, L.A.; Rosenheck, R. Gender Differences in the Prevalence of Fibromyalgia and in Concomitant Medical and Psychiatric Disorders: A National Veterans Health Administration Study. *J. Women's Heal.* 2018, 27, 1035–1044.
25. Heredia-Jimenez, J.; Orantes-Gonzalez, E. Gender differences in patients with fibromyalgia: A gait analysis. *Clin. Rheumatol.* 2018, 38, 513–522.
26. Úbeda-D'Ocasar, E.; Gallego-Sendarrubias, G.M.; Guodemar-Pérez, J.; Hervás-Pérez, J.P. Differences Between Men and Women with Fibromyalgia. *Phys. Med. Rehabil. Kurortmed.* 2020.
27. Garrido, M.; Castaño, M.; Biehl-Printes, C.; Gomez, M.; Branco, J.; Tomas-Carus, P.; Rodriguez, A. Effects of a respiratory functional training program on pain and sleep quality in patients with fibromyalgia: A pilot study. *Complement. Ther. Clin. Pr.* 2017, 28, 116–121.
28. Torgrimson-Ojerio, B.; Ross, R.L.; Dieckmann, N.F.; Avery, S.; Bennett, R.; Jones, K.D.; Guarino, A.J.; Wood, L.J.; Dieckmann, N.F. Preliminary evidence of a blunted anti-inflammatory response to exhaustive exercise in fibromyalgia. *J. Neuroimmunol.* 2014, 277, 160–167.
29. Álvarez-Gallardo, I.C.; Bidonde, J.; Busch, A.; Westby, M.; Kenny, G.P.; Delgado-Fernández, M.; Carbonell-Baeza, A.; Rahman, P.; De Angelis, G.; Brosseau, L. Therapeutic validity of exercise interventions in the management of fibromyalgia. *J. Sports Med. Phys. Fit.* 2019, 59, s0022–s4707.
30. Alp, A.; Oral, A.; Ocakoğlu, G.; Dirican, M.; Yurtkuran, M. Evidence of Defective Growth Hormone Response and Adaptive Hormonal Changes in Fibromyalgia. *Phys. Med. Rehabil. Kurortmed.* 2014, 24, 14–20.
31. De Oliveira, F.R.; Gonçalves, L.C.V.; Borghi, F.; Da Silva, L.G.R.V.; Gomes, A.E.; Trevisan, G.; De Souza, A.L.; Grassi-Kassisse, D.M.; Crege, D.R.X.D.O. Massage therapy in cortisol circadian rhythm, pain intensity, perceived stress index and quality of life of fibromyalgia syndrome patients. *Complement. Ther. Clin. Pr.* 2018, 30, 85–90.
32. Pernambuco, A.P.; Carvalho, L.D.S.C.; Schetino, L.P.L.; Polese, J.C.; Viana, R.D.S.; Reis, D.D. Ávila Effects of a health education program on cytokines and cortisol levels in fibromyalgia patients: A randomized controlled trial. *Adv. Rheumatol.* 2018, 58, 21.
33. Freitas, R.P.D.A.; Lemos, T.; Spyrides, M.H.C.; De Sousa, M.B.C. Influence of cortisol and DHEA-S on pain and other symptoms in post menopausal women with fibromyalgia. *J. Back Musculoskelet. Rehabil.* 2012, 25, 245–252.
34. Riva, R.; Mork, P.J.; Westgaard, R.H.; Rø, M.; Lundberg, U. Fibromyalgia Syndrome is Associated with Hypocortisolism. *Int. J. Behav. Med.* 2010, 17, 223–233.
35. Stehlik, R.; Ulfberg, J.; Zou, D.; Hedner, J.; Grote, L. Morning cortisol and fasting glucose are elevated in women with chronic widespread pain independent of comorbid restless legs syndrome. *Scand. J. Pain* 2018, 18, 187–194.

36. Basavakumar, D.; Flegg, M.; Eccles, J.A.; Ghezzi, P. Accuracy, completeness and accessibility of online information on fibromyalgia. *Rheumatol. Int.* 2019, 39, 735–742.
37. Gur, A.; Cevik, R.; Sarac, A.J.; Colpan, L.; Em, S. Hypothalamic-pituitary-gonadal axis and cortisol in young women with primary fibromyalgia: The potential roles of depression, fatigue, and sleep disturbance in the occurrence of hypocortisolism. *Ann. Rheum. Dis.* 2004, 63, 1504–1506.
38. Bonnabesse, A.L.F.; Cabon, M.; L'Heveder, G.; Kermarrec, A.; Quinio, B.; Woda, A.; Marchand, S.; Dubois, A.; Giroux-Metges, M.-A.; Rannou, F.; et al. Impact of a specific training programme on the neuromodulation of pain in female patient with fibromyalgia (DouFiSport): A 24-month, controlled, randomised, double-blind protocol. *BMJ Open* 2019, 9, e023742.
39. Roerink, M.E.; Roerink, S.H.P.P.; Skoluda, N.; Van Der Schaaf, M.E.; Hermus, A.R.; Van Der Meer, J.W.; Knoop, H.; Nater, U.M. Hair and salivary cortisol in a cohort of women with chronic fatigue syndrome. *Horm. Behav.* 2018, 103, 1–6.
40. Papandreou, M.; Philippou, A.; Taso, O.; Koutsilieris, M.; Kaperda, A. The effect of treatment regimens on salivary cortisol levels in patients with chronic musculoskeletal disorders. *J. Bodyw. Mov. Ther.* 2019, 24, 100–108.
41. Tak, L.M.; Cleare, A.J.; Ormel, J.; Manoharan, A.; Kok, I.C.; Wessely, S.; Rosmalen, J.G. Meta-analysis and meta-regression of hypothalamic-pituitary-adrenal axis activity in functional somatic disorders. *Biol. Psychol.* 2011, 87, 183–194.
42. Herane-Vives, A.; Papadopoulos, A.; De Angel, V.; Chua, K.-C.; Chalder, T.; Young, A.H.; Cleare, A.J. Cortisol levels in chronic fatigue syndrome and atypical depression measured using hair and saliva specimens. *J. Affect. Disord.* 2020, 267, 307–314.
43. Riva, R.; Mork, P.J.; Westgaard, R.H.; Lundberg, U. Comparison of the cortisol awakening response in women with shoulder and neck pain and women with fibromyalgia. *Psychoneuroendocrinology* 2012, 37, 299–306.
44. Geiss, A.; Rohleder, N.; Anton, F. Evidence for an association between an enhanced reactivity of interleukin-6 levels and reduced glucocorticoid sensitivity in patients with fibromyalgia. *Psychoneuroendocrinology* 2012, 37, 671–684.

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