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.

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 (ACTTION-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 adrenocorticotropic 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 though 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 [1] 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.

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