

One year in review 2021: fibromyalgia

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ABSTRACT

Fibromyalgia (FM) is a syndrome of unknown aetiology characterised by chronic pain, fatigue, and disturbed sleep. This review presents and summarises the 2020 literature on FM by retrieving all articles indexed in PubMed between 1 January 2020 and 31 December 2020. The attention of the scientific community towards FM is constantly growing, and this year's review is focused on the diagnostic, pathogenetic and therapeutic aspects of this syndrome. In particular, the treatment options for FM, both pharmacological and non-pharmacological, have been extensively studied.

Introduction

Fibromyalgia (FM) is a chronic pain syndrome characterised by widespread musculoskeletal pain, extreme fatigue and sleep disturbances, that has a prevalence of 1-5% (1). Neuropsychiatric manifestations such as cognitive impairment, and mood and anxiety symptoms or syndromes are also observed. FM can have a profoundly negative physical and psychological impact on the patients' lives, and many patients are physically disabled and experience a dramatically impaired quality of life (QoL) (2). Every year, new data on pathogenesis, epidemiology, genetic and treatment of FM are available for improving the management of these patients. As in all annual reviews focused on FM (3-6), in this paper we selected the most recent and relevant publication on pathogenesis, clinical manifestations and treatment strategies of FM. We performed a Medline search in PubMed database with the following key words: "fibromyalgia", "fibromyalgia syndrome", "pharmacological therapy", "non-pharmacological treatment", "pathogenesis", "epidemiology". The literature review has

been limited to the articles published in PubMed database from January to December 2020.

Epidemiology

A population-based multicentre study (7) found a fibromyalgia (FM) prevalence of 2.45% in an adult Spanish sample, a rate very similar to that observed in Europe as a whole (2.64%). The variables associated with the development of FM (female sex, age between 60 and 69 years, low socio-economical level, and obesity) are consistent with the findings in the literature.

Diagnosis and clinimetric assessment

Starting from 1990, when the American College of Rheumatology (ACR) first approved the criteria for FM, many efforts have been made to create diagnostic criteria that are able to capture the multi-faceted clinical reality of FM. The first ACR criteria required the presence of chronic widespread musculoskeletal pain (>3 months) and evocable tenderness on palpation in at least 11 out of 18 specified tender points (8). In 2010, the ACR preliminary diagnostic criteria (ACR 2010 Cr) (9) eliminated the need for eliciting tender points (TPs) and introduced the Widespread Pain Index (WPI), and the Symptom Severity Scale (SSS) to measure the manifold associated symptoms. In 2011, the ACR 2010 Cr was modified to eliminate the need for an interviewer and allow epidemiologic studies (ACR 2011 Cr) (10). A further revision (ACR 2016 Cr) (11) added the generalised pain criterion (pain in at least four of five regions), specified somatic symptoms including headache, pain or abdominal cramps, and depression, also stating that a diagnosis of FM does not exclude the presence of other diagnoses.

Recently, the Analgesic, Anesthetic, and Addiction Clinical Trial Transla-

tions Innovations Opportunities and Networks (ACTION)-American Pain Society (APS) Pain Taxonomy (AAPT) introduced new criteria focusing on:

1) six or more pain sites from a total of nine, 2) moderate-to-severe sleep problems or fatigue, and 3) multisite pain plus fatigue or sleep problems present for at least three months.

Salaffi *et al.* (12) compared the concordance of ACR 2011 Cr, ACR 2016 Cr and AAPT Cr in the diagnosis of FM, and explored the performance of an additional set of criteria: the modified Fibromyalgia Assessment Status (FAS 2019 modCr). The study demonstrated that the ACR 2011 Cr offer the best performance when compared with clinical judgment, while the AAPT Cr the worst. The modified FAS provided a diagnostic accuracy comparable to that provided by the other diagnostic criteria evaluated.

Galvez-Sánchez *et al.* (13) critically reviewed of the ACR Diagnostic Criteria for FM and pointed out a series of limitations of the ACR criteria from 2010 to 2016, in particular the persistence of a considerable FM misdiagnosis rate in the general population and the lack of sufficient recognition of psychological, environmental, and sociocultural factors. The authors underscored the possibility of incorporating some objective measures associated with FM pathophysiology to increase diagnosis reliability and validity.

However, beyond the set of criteria used, the diagnosis of FM is still challenging, especially in primary care. To address the need to improve the identification of FM in daily clinical practice, Salaffi *et al.* (14) developed and tested a new six-item self-administered tool, the Simple Fibromyalgia Screening (SIFIS) questionnaire. A cut-off of 4 (4/yes) gave the highest correct identification rate (78.9%), with a sensitivity of 89.4% and a specificity of 77.5%. A second FM screening tool was developed based on the self-report Multidimensional Health Assessment Questionnaire (MDHAQ), which has been found informative in most of the rheumatic diseases studied. Cumulative indices of 3 or 4 MDHAQ measures were analysed as fibromyalgia as-

essment screening tools (FAST). They were shown to correctly identify most patients who meet ACR2011Cr, indicating the presence of comorbid FM, without the need for using a separate specific questionnaire (15).

A common complaint of patients with FM is a soreness, but no assessment tool is available to address it and evaluate its impact on disease severity. Chang *et al.* (16) developed and tested a revised version of the FIQR, the “Fibromyalgia Impact Questionnaire Revised with Integration of Soreness Sensation (FIQRS)”, by adding five items pertaining to soreness to the existing FIQR. The study indicated that soreness can be identified with this questionnaire with good test-retest reliability and internal consistency.

Pathogenesis

The pathogenesis of FM is still unclear, but there is evidence of the involvement of mast cells (MCs) (connective tissue immune cells) and their products, such as tumour necrosis factor (TNF), interleukin (IL)-1 and IL-6, which cause hyperalgesia in rodents. In addition, there is evidence of corticotropin-releasing hormone (CRH) and substance P (SP) production by neurons (17). CRH and SP, in turn, activate MCs to release neuro-sensitising pro-inflammatory substances that can maintain and exacerbate a low-grade chronic inflammation. However, MCs also released IL-37 which prevents inflammation and exerts therapeutic activity on damaged tissues by inhibiting the inflammation.

The review of Banfi *et al.* (18) focused on the role of T cells in the physiopathology of FM. Despite the number of studies reporting an altered frequency and/or polarisation of T cells (mainly CD4+ T cells) in patients with FM, the literature reviewed provided inconclusive results about the role of T cells. However, a new perspective has been provided by a mouse model of acute stress exposure showing that CD4+ T cells are essential for the onset and development of stress-induced anxiety behaviours.

Several studies have reported an association between reduced levels of 25

hydroxyvitamin D3 (25(OH)D3) and chronic pain in patients with arthritis and FM. A systematic review (19) concluded that despite the dubious relationship between FM and vitamin D, a supplementation therapy with doses from 1200 IU daily to a single dose of 600.000 IU produced an improvement in pain perception and musculoskeletal hypersensitivity in 6 out of 9 studies.

The relationship between an anti-inflammatory diet and pain hypersensitivity has been investigated using the Dietary Inflammatory Index (DII), a validated measure of patient inflammation levels calculated by conducting a 24-hour diet recall interview. The study of Correa-Rodriguez *et al.* (20) revealed that in women with FM, the pressure pain thresholds (PPTs) of TPs, but not pain, fatigue, sleep, and anxiety, were associated with DII score.

Overweight and obesity are highly prevalent in FM. Leptin, an appetite-regulating hormone, growth hormone (GH), and insulin-like growth factor (IGF-1) are weight-related hormones found altered in patients with FM. The study by Koca *et al.* (21) demonstrated that GH and IGF-1 levels were significantly lower and leptin significantly higher in patients with FM than in healthy controls. The levels of the three hormones were independent of disease severity but correlated with BMI in the FM group.

Sarzi-Puttini *et al.* (22), in their update on clinical characteristics, aetiopathogenesis and treatment of FM, highlighted that the functional neuroimaging studies are beginning to reveal the neurophysiological mechanisms of FM, and their interaction with socio-environmental stressors, creating a putative aetiopathogenetic model that sees the coexistence of top-down (central to peripheral) and bottom-up (peripheral to central) mechanisms.

In the last decade, several studies have suggested the involvement of small fiber neuropathy (SFN) in the pathogenesis of FM. In their review, Ghasemi *et al.* (23) concluded that the recent findings suggest that patients with FM reside along a continuum between purely peripherally induced pain, with a recognised SFN, and a purely centrally induced pain.

A recent method for diagnosing SFN is laser-evoked brain potentials (LEP), which allow the functional assessment of the thermo-nociceptive system, including the evaluation of SFN. A retrospective study (24) showed no signs of a damaged thermo-nociceptive system in 92 patients with FM compared with 39 healthy controls, not supporting the hypothesis that SFN is a significant contributor to the pathophysiology of FM. Albeit the pathophysiological mechanism of SFN is still unclear, recent studies supported the role of keratinocytes and fibroblasts in the nociceptor function, due to their activity in secreting algescic mediators, cytokines and axon guidance cues, and in expressing many nociception-associated ion channels. The prospective study of Evdokimov *et al.* (25) found higher gene expression of transforming growth factor- β 1 (TGF- β 1), hyperpolarisation-activated cyclic nucleotide-gated ion channel-2 (HCN2), and axon guidance molecules EFNA4 (with their main receptor EPHA4) in fibroblasts, and of IL-10, EFNA4, and EPHA4 in keratinocytes of patients with FM compared to healthy controls. The gene expression of other proinflammatory cytokines (IL-1 β , IL-6, IL-8, TNF- α) did not differ between FM patients and healthy controls.

In recent decades, there has been growing evidence of the role of the gut microbiome in the pathogenesis of several medical conditions, including FM. In their review, Minerbi and Fitzcharles (26) described an altered gut bacterial composition and an abnormal microbe metabolic function in individuals with FM. However, it is still unclear whether these changes have a pathogenetic role in FM, and if the manipulation of the microbiome could impact on FM symptoms.

A systematic review on this topic has been made by Erdrich *et al.* (27), who identified five broad areas of research with papers reporting on *Helicobacter pylori*, other gut bacterial markers and metabolomics, including intestinal permeability and small intestinal bacterial overgrowth. Despite the limitations of the included studies, associations emerged between composition

and metabolism of the gastrointestinal microbiota and FM, as well as preliminary findings of the effectiveness of gastrointestinal microbiome-targeted interventions in improving clinical symptoms and/or laboratory measures related to FM.

Genetic aspects

Several studies have suggested that FM has a familial component. Using genome-wide association studies (GWAS) data, Dutta *et al.* (28) investigated the genetic heritability of a continuous measure of FM severity, the FM score, calculated by summing the WPI and SSS. The study demonstrated that younger individuals (≤ 50 years) appear to have a much stronger genetic component to the FM score than older individuals, who were more likely to have autoimmune or structural causes of pain. It is now clearly recognised that 45% of the human genome, constituted by transposable elements (TEs) (DNA sequences that move from one location on the genome to another), is transcriptionally active. Dysregulation of TEs, including human retroviral endogenous sequences (HERVs), has been shown to associate with several diseases, including Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), a disease frequently comorbid with FM. The study by Ovejero *et al.* (29) showed that HERVs are overexpressed in immune cells of FM patients with or without comorbid ME/CFS, and that FM patients with increased HERV expression presented increased levels of interferon β and γ (INF- β and INF- γ). These findings could explain the flu-like symptoms that often occur in FM patients in the absence of concomitant infections.

Psychological aspects

Psychological aspects are relevant for the management of FM. Two studies focused on alexithymia, a personality trait highly prevalent in patients with FM (20-44%), characterised by a difficulty in identifying, and expressing subjective feelings and in distinguish between feelings and the emotional arousal-related physical sensations. Horta-baas *et al.* (30) investigated the relationship between alexithymia and

pain, fatigue, health-related quality of life, sleep quality, depression, anxiety, and disability. The study revealed that alexithymia was significantly associated with increased perceptions of disability and worse perception of the psychological and social dimensions of quality of life, independently of other variables.

The review by Alslman *et al.* (31) focused on the role of alexithymia in adolescents with FM. The reviewed studies agreed in detecting a strong association between FM and psychological distress, such as anxiety and depression in adolescents, and, as proposed for adult FM patients, a possible relationship was suggested between alexithymia and FM, as well as a mediating effect of psychological distress on this relationship.

Among the psychological aspects, personality features are thought to play a role in predisposing to FM development. The Minnesota Multiphasic Personality Inventory-2 (MMPI-2), which is used to assess clinical and personality psychopathology, yields five scales (PSY-5): Aggressiveness, Psychoticism, Disconstraint, Negative Emotionality/Neuroticism, and Introversion/Low Positive Emotionality. In a cross-sectional assessment of 56 females with FM (32), MMPI-2 identified two clusters of clinical levels of psychopathology and personality dimensions. The largest cluster had no clinically significant elevation of any psychopathology scale. In contrast, the other cluster had clinically significant elevations of the Negative Emotionality scale that hinders relationships with others, and the Introversion scale that leads to emotional and social disengagement.

Hirsch *et al.* (33) explored the psychological construct of the "silver lining", which refers to the ability to believe in a positive side of the illness, despite the negative consequences of being ill. In a sample of 401 individuals with FM, the study demonstrated that a perceived silver lining weakened the association between FM impact and depressive symptoms, as previously found in multiple sclerosis, cancer, cardiac and renal diseases.

Comorbidities

Studies converge to indicate that FM is strongly associated with several mental and physical illnesses. The wave III (2012–2013) of the US National Epidemiologic Survey on Alcohol and Related Conditions (NESARC-III) (34), assessed the prevalence of self-reported FM at 2.05%. Based on a structured, computer-assisted diagnostic interview, participants with self-reported FM, compared with those without FM, were more likely to be divorced/separated women with lower incomes, and to present at least one lifetime mental disorder (adjusted odds ratio [aOR]=2.32), mostly mood disorder (aOR=2.27) and anxiety disorders (aOR=2.81). Moreover, participants with self-reported FM had a higher past 12-month prevalence of physical disorders, in particular cancer, dyslipidaemia, diabetes, and cardiovascular disease, than their counterparts without FM (100% and 57.17%, respectively). Population and clinical studies suggested that the comorbidity between bipolar mood disorder (BD) and panic disorder (PD) marks a specific subtype of BD. The study by Alciati *et al.* (35) showed that the comorbidity between BP and PD expresses in FM patients at higher rates than in general population and psychiatric outpatient samples. The comorbid BD/PD appeared to precede or develop concurrently with FM in nearly 80% of the patients. Therefore, it cannot be interpreted as reactive to the presence of symptoms/functional impairment produced by FM, but rather as a predisposing factor.

FM can present as a primitive syndrome (PFM) or as a condition associated with rheumatological diseases due to structural pathology, particularly rheumatoid arthritis (RA). The comparison of psychiatric comorbidities and life adversities between a group of patients with PFM and a group with FM associated with RA (SFM), revealed that the lifetime rates of major depression and PD, as well as the rates of childhood sexual abuse and physical neglect, were significantly higher in PFM *versus* SFM. In the logistic regression model, lifetime PD and childhood physical neglect remain as independent risk factors for PFM (36).

Take-home messages

- FM pathogenesis is still unclear, but there is evidence of the involvement of mast cells (MCs) (connective tissue immune cells) and their products, such as tumour necrosis factor (TNF), interleukin (IL)-1 and IL-6, which cause hyperalgesia in rodents. Several studies have reported an association between reduced levels of 25 hydroxyvitamin D3 (25(OH)D3) and chronic pain in patients with arthritis and FM.
- Studies converge to indicate that FM is strongly associated with several mental and physical illnesses. Moreover, psychological aspects are relevant for the management of FM.

Treatment of fibromyalgia

It is known that the bioactive lipid lysophosphatidic acid (LPA) and LPA1 receptors are involved in the initiation of neuropathic pain (NeuP) and in FM-like mouse models, as suggested by the abolition of abnormal pain in LPA1 receptor-KO mice. The experimental evidence for the efficacy of antagonists of lysophosphatidic acid (LPA) receptors in treating chronic pain in mice models opens the way for possible therapeutic applications (37).

Protocols

The paper by Araya-Quintanilla *et al.* (38) reported the protocol of a single-blinded, randomised controlled trial aimed at assessing the effectiveness of the multi-component treatment *versus* conventional treatment in women with FM. The intervention group is to receive a multi-component treatment based on physical exercise, cognitive behavioural therapy (CBT) adding to a Graded Motor Imagery (GMI), and a Therapy Neuroscience Education (TNE) programme, whose aim is to facilitate sensory and motor cortex reorganisation. In the control group, all patients are to receive pharmacotherapy and a conventional treatment programme based on standard education by the physician.

Multi-component treatments are defined as an integration of exercise therapy (ET), cognitive behavioural therapy (CBT), and pharmacological treat-

ment, and have generally been favourably used in the management of FM patients. The Nature Activity Therapy for people with Fibromyalgia (NAT-FM) project includes a range of treatments that integrates CBT, ET, Pain Neuroscience Education (PNE) and nature exposure. The study protocol of an RCT published in 2020 compared this approach to the treatment as usual (TAU) on FM pain and symptoms (39). A total of 160 patients with FM will be recruited and randomised into two groups (TAU and TAU+NAT-FM). The patients in the TAU group will continue to receive the same drugs used at the enrolment. Primary outcome measures will be the Revised Fibromyalgia Impact Questionnaire (FIQR), while the secondary outcomes will include questionnaires for specific aspects of the life of FM patients (39). Based on the results, this RCT could lead to the inclusion of NAT-FM in the current management of FM.

Pharmacological therapy

Cannabinoids

Cannabis acts throughout its psychoactive substance, defined as tetrahydrocannabinol (THC), on brain receptors called endocannabinoid receptors. A review published this year (40) focused on using cannabis in chronic pain due to its positive effect on pain perception and the immune system. However, only two randomised controlled clinical trials (RCTs) included exclusively patients with FM (40). A retrospective study conducted in Washington State pointed out that FM was the diagnosis for the prescription of medical cannabis in 14% of patients (41), while in Canada 34% of 5452 patients prescribed with cannabinoids had a diagnosis of FM (42). In 2008, a randomised double-blind placebo-controlled study evaluated the effectiveness of nabilone, a cannabinoid commercialised in the United States, in 20 patients with FM (43). All patients in this group showed a greater decrease in pain measured with the Visual Analogue Scale (VAS), in Fibromyalgia Impact Questionnaire (FIQ) and anxiety scores, but a higher percentage of side effects than in the control group. A crossover study com-

pared nabilone to amitriptyline (10 mg) in treating insomnia in FM patients, finding no significant improvement in pain, mood, or quality of life in the nabilone group (44). In a single-centre observational study conducted on 102 FM patients, treatment with cannabis oil extracts was associated with significant improvement in the FIQR score in 44% of patients and the Pittsburgh Sleep Quality Index (PSQI) in 33% of patients (45). A cohort study involving 367 FM patients showed that medical Cannabis was associated in 81.1% of cases with the achievement of treatment response, defined as at least moderate or significant improvement in a patient's condition at six months of follow-up without the cessation of treatment or severe side effects (46). On the contrary, a recent randomised placebo-controlled crossover trial carried out on 20 patients with FM, and using four different varieties of inhaled pharmaceutical-grade cannabis, found that the active treatment did not seem to affect pain scores (47). As seen, the body of evidence for medical cannabis treatment in FM patients is inconclusive, but on different polls and online questionnaires, a large proportion of patients using cannabis report improvement in both pain and quality of life (40). Particular attention must be observed in patients with underlying psychological conditions since cannabis use has been linked with a higher incidence of psychosis, memory impairment, developmental and cognitive disorders (48).

Naltrexone

Naltrexone is an orally active opioid receptor antagonist, primarily used to treat opioid and alcohol addiction. In FM, naltrexone could act as improving opioid signalling, exerting an anti-inflammatory effect, and increasing levels of both endorphin and met-enkephalin. A single-centre study aimed to determine the dose of naltrexone effective in 50% (ED50) and 95% (ED95) (49) of 25 females with FM who received a dosing interval ranging from 0.75 mg to 6 mg. No serious adverse events occurred, but side effects were common, such as severe nausea, abdominal pain and headache. The au-

thors estimated the ED50 to be 3.88 mg and the ED95 to be 5.40 mg. Based on these findings, a dose of 4.5 mg seems to be a reasonable test dose in FM patients, as it lies in the range between the ED50 and ED95 (49).

Lidocaine

Lidocaine, a drug that exerts analgesic and anti-inflammatory effects by blocking sodium channels in the neuronal cell membrane, was used for refractory symptoms of FM. Also, intravenous magnesium has shown a beneficial impact on neuropathic back pain and postherpetic neuralgia. On these premises, a study aimed to establish an effective dose of intravenous (IV) lidocaine in FM treatment, with magnesium added to the highest dose of lidocaine (50). A total of 74 FM patients received a lidocaine infusion once every two months. During the first infusion, every patient received 5 mg/kg of lidocaine. After that, if the patient had >25% pain relief for less than two weeks, the dose was escalated, reaching 7.5 mg/kg, or magnesium added up to 7.5 mg/kg of lidocaine plus 2.5 magnesium sulfate. This study shows that lidocaine infusions safely and effectively reduce pain in a significant number of patients diagnosed with FM refractory to other conventional therapies, with higher dosage producing a greater analgesic response. The adjunct of magnesium sulfate did not seem to have a clear statistically significant benefit (50).

Tramadol

Analgesics play an important role in pain relief in FM patients. Tramadol is a weak opioid, and the action on serotonin reuptake inhibition mediates its efficacy. A systematic review of RCTs evaluating the effectiveness of tramadol alone or in combination with antidepressant or analgesic on FM symptoms was published in 2020 (51). Using a VAS scale, the reduction of pain was demonstrated by three out of the four RCTs included. Tramadol combined with the analgesic acetaminophen was associated with improved quality of life compared to placebo, while tramadol alone against placebo did not show the same benefit. Tramadol combined with an

antidepressant or an analgesic did not significantly affect sleep quality or depressive symptoms. In the fourth trial included, a single-dose treatment with 100 mg/2 mg intravenous tramadol did not show any significant effect on pain relief compared to placebo, in a cross over design. This review did not find enough evidence to support the use of tramadol in FM patients (51).

Non-pharmacological therapy

Mindfulness

Mindfulness is defined as being conscious of the present moment without judgment, accepting feelings, thoughts, and bodily sensations. FM patients with higher mindfulness generally have better psychological health and sleep quality as well as less pain. Scientific literature identified five mindfulness components: observing, describing, acting with awareness, non-judging, and non-reacting (52).

A study carried out using a secondary cross-sectional analysis of data from a randomised controlled trial comparing Tai Chi and aerobic exercise examined the association between mindfulness, sleep quality, and FM symptoms (53). The ability to be mindful was measured in 177 patients with FM using the Five Facet F Mindfulness Questionnaire (FFMQ), a validated 39-item self-report instrument. Higher total mindfulness was significantly associated with better sleep, less pain interference and lower depressive and anxiety symptoms scores. Mindfulness was significantly correlated with sleep quality, and this relationship was mediated considerably by pain interference, depression, and anxiety. These results prompted the authors to suggest a more holistic approach to clinicians when treating FM patients (53).

Acupuncture

Complementary treatments, including acupuncture and nutraceutical supplementation, are often used in addition to pharmaceutical therapy in FM patients. A prospective randomised controlled clinical trial was conducted to compare the efficacy of acupuncture and nutraceutical supplementation with Migratens®, a food supplement

containing coenzyme Q10, vitamin D, alpha-lipoic acid, magnesium, and tryptophan (54). Sixty female patients with FM were randomised to receive either Migratens (1 sachet twice daily for 12 weeks), or an acupuncture treatment performed according to traditional Chinese medicine principles (TCM) by the same licensed operator. In the Migratens group, the VAS pain score change was statistically significant at T1 (1 month after the start of treatment) and at T2 (3 months after the start of treatment). In contrast, no statistically significant change was present at T3 (6 months after the start of treatment and 3 months after treatment interruption). In the acupuncture group, the VAS score change was statistically significant at T1, T2 and T3. Regarding secondary endpoints, in the Migratens group, the change in FIQR and FSS scores was not statistically significant at T1, T2 and T3, while in the acupuncture group, the change in FIQR and FSS scores was statistically significant at T1, T2 and also at T3. The reduction in both the primary and secondary endpoints was more significant in the acupuncture group, but positive results were obtained in both treatment groups (54).

Physical therapy: kinesio taping (KT)

FM management often includes several physical therapies, and one of the foremost is kinesio taping (KT). KT works by improving muscle contraction, reducing fatigue, ameliorating fluid congestion and normalising the fascia muscle tone and abnormality. Spinal stabilisation exercises (SSE) consist of neuromuscular control and re-education of the deep postural spinal muscles and are considered primary interventions in treating chronic pain. A randomised study compared the effects of 6-week SSE plus KT or SSE alone treatments in 36 women with FM (55). SSE alone reduced pain and depression and improved health status, quality of life, and sleep quality. The decrease of fascial dysfunctions using KT with the fascial correction technique can explain these results. Therefore, the KT application may be considered a non-pharmacological and complementary therapy for FM (55).

Physical exercise

A large amount of evidence from the literature shows that physical exercise determines improvement in FM symptoms, leading to better pain modulation, sleep quality, quality of life and lower rates of depression. A study that enrolled 284 patients with FM (56) collected data on sociodemographic characteristics, mode and weekly frequency of physical exercise via self-reported questionnaires. Compared with patients who did not exercise, those who exercised regularly had a better quality of life ($p=0.007$), higher well-being scores ($p=0.007$), fewer days missing from work ($p=0.048$) and lower depression levels ($p=0.001$), demonstrating the key role of exercise in the control of FM symptoms (56).

Manual therapy

Manual therapy is a physiotherapeutic practice consisting of manipulating joints, connective and subcutaneous tissues, and skin to increase mobility, relieve pain and rehabilitate the function. Despite the extensive use of this practice in patients with FM, the benefit of massage in FM is not fully established, and some types of massage can be too painful. A study aimed to establish the effect of pressure massage on connective tissue at the back of the neck on pain and other symptoms, such as sleep, anxiety, and fatigue (57). A total of 24 patients diagnosed with FM were randomised to receive digital manual therapy on the posterior cervical musculature or placebo, consisting of an ultrasound session in the same area. The patients presented homogeneous values at the initial evaluation, while the *post hoc* analysis showed a decrease in the pain scale between pre- and post-intervention in the manual therapy group (MD: 4.223, $p<0.001$, ES: 2.072). The authors concluded that there is a possible benefit of manual therapy on the pain experienced by FM patients, but they also underlined that this therapy should be administered by an expert physiotherapist to avoid eliciting pain (57).

Electrotherapy

In 2020 a systematic review was published on the use of electrotherapy, a

term defining a vast number of electrical therapeutic modalities for muscle stimulation and analgesia, in FM patients (58). An RCT conducted by Dailey (59) showed that four weeks of TENS provided a reduction in pain evoked by movement and fatigue, with significantly few side effects compared to placebo.

Non-invasive brain stimulation techniques are used to modify the excitability of some brain regions. The most widely studied techniques are transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS). In FM, to obtain pain relief, tDCS is often applied in the primary motor cortex area (M1). Repeated tDCS sessions can lead to neuroplasticity and neuronal excitability changes, as pointed out in a study by Castillo-Saavedra *et al.* that proposed 3 weeks as a proper target (60). On this matter, Brietzke *et al.* found that 20 sessions of home-based tDCS over dorsolateral prefrontal cortex provided 45.65% improvement in the cumulative pain scores, increasing to 62.06% when extended to 60 sessions (61).

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive technique that modulates cortical and deep brain areas' excitability through electrical current pulses. A study by Altas *et al.* (62) analysed the effectiveness of 15 sessions of high-frequency rTMS over two distinct brain areas in patients with FM, demonstrating that the pain relief effect was higher when the TMS was applied over the left primary motor cortex. Still, this effect was also present in the placebo group, as also observed by Avery *et al.* (63). LASER is usually applied to tender points, providing benefits in relieving pain and decreasing the number of tender points. Other types of electrotherapy used with favourable outcomes in patients with FM include the occipital nerve field stimulation with direct current through subcutaneous electrodes, thus activating the descending pain inhibitory pathway (64).

The authors of the review concluded that non-invasive brain stimulation, TENS, and LASER are electrotherapy techniques that can be used in FM for their

positive effects on pain, even if they lack a standardised administration protocol. Another meta-analysis of fourteen studies, for a total of 452 participants, focused on the clinical impact of anodal tDCS for the treatment of pain in FM patients. The meta-analysis results show that active tDCS *versus* sham reduce pain intensity (65).

Pilates

Pilates is an exercise method which aims to improve general body flexibility, core strength and posture. In a single-blind RCT (66), 42 women with FM were randomised into the Mat Pilates group (MP; n=21) and the Aquatic Aerobic Exercise group (AAE; n=21), and then evaluated at baseline and after 12 weeks. FIQ and VAS pain scores showed statistically significant improvement in both groups. The MP group also showed improvements in quality of life (vitality, functional capacity and pain domains of the SF-36). For the AAE, there were improvements in PSQI total ($p=0.02$) and in Pain-Related Catastrophising Thoughts Scale (PRCTS) ($p=0.01$) (66). The Pilates method is a recommended form of exercise for healthy individuals, but it can also lead to a better quality of life and pain reduction in FM patients, similarly to aerobic exercise.

Zumba dancing

Zumba dancing is a mixture of dance and aerobic, rapid, and balanced movements, which is thought to improve flexibility and motor function in healthy individuals and FM patients. In a study conducted in 2020 (67), 60 subjects were divided into three groups, Zumba dancing, aerobic exercise training and a control condition. Patients in Zumba dancing and aerobic exercise training conditions showed a significant increase in motor function and decrease of depressive symptoms, with a greater improvement in the Zumba group, while in the control group, motor function and depression scores remained unchanged (67).

Tryptophan and magnesium

Micronutrients contained in food have been commonly used as supplementa-

tion to treat FM symptoms, in particular tryptophan (TRY), an essential amino acid precursor of serotonin and magnesium (MG). In a 16-week study, twenty-two middle-aged women with FM were randomised to receive a Mediterranean diet (high quantity of vegetables and reduced intake of meat) with supplementation of 60 mg of TRY and 60 mg of MG, and an iso-caloric standard Mediterranean diet (control group) (68). At the end of the observation, tryptophan and magnesium-enriched Mediterranean diet reduced fatigue, anxiety and mood symptoms, eating disorders, and dissatisfaction with body image but did not improve sleep quality in women with fibromyalgia (68).

Isokinetic exercise

A study was performed in order to compare functional and isokinetic performance between 20 women with FM and a control group of 20 women of the same age (69). In the FM group, there were impaired functional performances at the 6-minute walking test (6MWT) ($p<0.001$) and the Chair Stand Test ($p<0.001$), showing lower muscle strength in the limbs and lower aerobic capacity, while the isokinetic performance presented no difference between the groups. The authors thus concluded that the functional performance of women with FM is worse compared with healthy women of the same age, underlying the importance of therapeutic exercises to improve these parameters in FM patients (69).

Functional training programme

Physical education and exercise have demonstrated to be effective in improving FM symptoms, but they are not often carried out for a long period of time by FM patients. A study conducted in 2020 aimed to analyse the effect of long-term physical training programmes on FM symptoms and quality of life (70). A total of forty women were randomised into an active group that performed continuous physical activity for nine years, and a control group that did not exercise regularly. The training programme consisted of 3 sessions per week of approximate-

ly 35–60-minute duration. After the follow-up period, the active group experienced a significantly better score in leg strength ($p<0.001$), handgrip strength ($p=0.009$), balance ($p=0.003$) and cardiorespiratory fitness ($p<0.001$) when compared to the control group. Improvements in the FIQ, number of tender points, algometer scale, and the VAS were demonstrated in women with FM who exercised regularly (70).

Music therapy

A recent review analysed the effect of music therapy in FM patients (71). Music therapy is defined as the use of music as part of a therapeutic procedure for improving communication, learning, mood and self-expression. Of the seven RCTs included in the meta-analysis, four examined the effects of music therapy on pain using the VAS, and two using the McGill Pain Questionnaire (MPQ). The pooled data showed a significant decrease in VAS after music therapy compared with a control group, while no significant differences in MPQ outcomes were noted, except for one study. The meta-analysis showed that music therapy reduced depressive symptoms (rated with BDI scores) in FM patients. No statistically significant differences were found in the FIQ scores between the intervention group and the control group (71). The significance of the meta-analysis was limited due to the low quality of the included studies, the small sample sizes and the high risk of deviation.

Dietary changes

Diet plays an important part in the management of FM patients. In fact, certain elements of nutrition can influence FM symptoms by modulating the oxidative status, inflammation, energy production and neuromodulation. A systematic review including 22 studies for a total of 806 patients (of which 97.94% were female), was carried out to analyse the effects of dietary changes on FM symptoms (72). In these studies, 17 different dietary interventions were used: the addition of coenzyme Q10, vitamin D, probiotics, Chlorella green algae, vegan diet, tart cherry juice, low-FODMAP diet, soy, extra-virgin olive

oil, caffeine, vitamin C, nigella sativa seeds, vitamin C, vitamin E, creatine, and acetyl-L-carnitine (64). This review concludes that there is insufficient evidence to recommend any particular dietary intervention in the management of FM symptoms (72).

Another review conducted on the dietary interventions in FM was published this year (73). All the included studies identified a beneficial effect of vitamin D supplementation, while results regarding vitamin C and vitamin E were inconsistent. Only few clinical trials analysed the effect of magnesium. One study did not demonstrate an effect on pain or depression, while the other, employing increased dose and a longer duration of magnesium treatment, showed a significant improvement in pain and tenderness. Probiotics were not associated with improvement in FM symptoms (73). Diet regimens implemented with extra virgin olive oil was associated with improvement in FIQ and mental health status in FM patients. The elimination of gluten was investigated in a pilot study on 97 women with FM and IBS, showing a slight but significant improvement of IBS and FM symptoms. A low-calorie diet was also associated with improvement in pain symptoms, sleep quality and depression, as well as a vegan diet. However, in this case the improvement in FM symptoms disappeared immediately after switching to an omnivorous diet (73).

Hyperbaric oxygen therapy

Hyperbaric oxygen therapy (HBOT) is a treatment in which a patient intermittently breathes 100% oxygen while in a chamber with a pressure two to three times greater than sea level. In 2004 an RCT which randomised 50 FM patients to receive 90-minute HBOT sessions or sham treatment, revealed a significant greater decrease in the number of tender points and pain thresholds in the HBOT group than in the sham treatment group. More recently, a prospective, active control trial randomly assigned 60 FM patients to treated and crossover groups, analysing the brain activity with the single-photon emission computed tomography (SPECT)

imaging. The treated group patients were evaluated at baseline and after HBOT and the crossover-control group patients were evaluated three times: baseline, after a control period of no treatment, and after HBOT. After forty 90-minute sessions with 100% oxygen at 2 ATA, HBOT significantly improved all FM symptoms and the quality of life in both groups, while the SPECT revealed a rectification of the abnormal brain activity in pain-related areas by means of inducing neuroplasticity (74). A prospective observational clinical trial conducted in Italy involved 32 patients with FM, who were treated with HBOT for three days per week for a total of twenty sessions (74). The patients who completed the sessions showed improvement in the scores of anxiety, fatigue and FM severity, but not in those of depression and quality of sleep. Another study analysed the effect of HBOT in 36 patients with primary FM, showing a significant effect on pain, fatigue, quality of life, mood and hours of sleep. Furthermore, by means of laboratory tests the authors reported a T helper 1 (Th1) activation of this subset which is modulated by HBOT (74).

Balneotherapy and hydrotherapy

Balneotherapy is defined as the use of natural mineral waters for bathing, drinking or inhalation, while hydrotherapy is the use of plain water as part of spa medicine. A randomised study conducted in 2020 was performed to compare the effectiveness of consecutive or intermittent balneotherapy in FM (75). The study included a total of 50 FM patients who received 20 minutes of full-body immersion in a heated plain water pool at 38°C, followed by the application of a heated mud pack on the back region. The consecutive group received treatment for 5 days a week for 2 weeks, while the intermittent group received treatment 2 times weekly for 5 consecutive weeks (75). In both the consecutive and intermittent groups, baseline pain severity significantly decreased in the post-treatment evaluations. After the first month, the percentage of patients reaching a 14% improvement in total score com-

pared with the baseline was 20% in the consecutive group, and 28% in the intermittent group. The decrease in FIQ did not reach a statistical significance, while significant improvements from baseline were observed in the patient's global assessment, physician's global assessment, and tender points count (75).

Take-home messages

- Studies reported a role cannabinoids, lidocaine and tramadol in the management of FM. The body of evidence for medical cannabis treatment in FM patients is inconclusive, but on different polls and online questionnaires, a large proportion of patients using cannabis report improvement in both pain and quality of life.
- Both pharmacological and non-pharmacological therapy, have been extensively studied and showed a role in FM.
- Among non-pharmacological therapy, in particular physical exercise determines improvement in FM symptoms, leading to better pain modulation, sleep quality, quality of life and lower rates of depression.

Conclusion

To conclude, the attention towards FM during 2020 focused on the diagnostic, pathogenetic and therapeutic aspects of this syndrome. The treatment options for fibromyalgia, both pharmacological and non-pharmacological, have been extensively studied. This review has summarised the most important results published in 2020 in order to provide to the clinicians and the experts in the field a helpful update.

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