INTRODUCTION

Fibromyalgia syndrome (FM) is a common chronic generalized musculoskeletal pain disorder, associated with systemic symptoms (e.g., mood disorders, fatigue, cognitive dysfunction, insomnia, and mood disturbances)***(Bellato et al., 2012).***

There are several suggested FM theories that can be classified into central and autonomic theories, such as a variety of neurotransmitters and neuroendocrine disturbances. These include reduced levels of biogenic amines, increased concentrations of excitatory neurotransmitters, as substance P, and dysregulation of hypothalamic-pituitary-adrenal axis ***(Hieblinger et al., 2009).***

FM can be triggered by multiple factors including psychological stress, medical illness as infections, and other polygenetic factors that are thought to be linked to the disease pathogenesis ***(Woolf, 2011).***

Vitamin D is postulated to play a role in the pathophysiology of FM- both centrally and peripherally ***(Karras et al., 2016).***

Centrally, vitamin D is thought to have a potential neuro-regulatory role, through promoting different nerve growth factors, besides having a neuroprotectiverole***(Rejnmark, 2011).***

Moreover, it is thought that vitamin D is associated with the synthesis of Glial cell line- derived neuronal growth factor (GDNF), a neuropeptide involved in protective actions regarding growth and maintenance of sympathetic and sensory neurons ***(Garcion et al., 2002).***

Peripherally, vitamin D seems to increase muscle strength through nuclear receptors in muscle tissue. Therefore, it is postulated that the chronic persistent pain of FM is associated with myopathy ***(Rejnmark, 2011).***

There are two recognized types of FM: Primary and secondary. The cause of primary FM is unknown. Secondary FM results from other diseases as rheumatic diseases (as rheumatoid arthritis, systemic lupus erythematosus and spondylonegativearthropathies), hypothyroidism and malignancy. In this type, treating the primary cause alleviates symptoms of FM ***(Wallace, 2003).***

The goals of FM treatment are to relieve the generalized pain, improve sleep quality, and improve physical activity through a reduction in associated symptoms as headache, fatigue and mood disorders ***(Benett et al., 2007).***

Treatment includes pharmacologic and non-pharmacologic treatment.

It is because of the complexity of pain and heterogeneity of FM patients that treating FM uses a multidisciplinary approach ***(Hassett et al., 2009).***

Non-pharmacologic treatment includes massaging, aerobic exercise which decreases tender points and increases overall well-being ***(Deare et al., 2013)***and Cognitive behavioral therapy (CBT), which enhances patients' beliefs in their own abilities and coping strategies ***(Theadom,2015).***

Pharmacologic therapy includes different pain medications as NSAIDs that have been used, but pain usually does not respond to them. Acetaminophen may ease the pain and stiffness caused by fibromyalgia ***(Jahan et al.,2012).*** Moreover, some medications are approved by FDA including pregabalin and duloxetine, however, only a minority of people; around 25%; achieved acceptably good pain relief with these lines of treatment ***(Wiffen et al.,2014).***

The European League Against Rheumatism (EULAR) gave the highest level of recommendation of “A” to a set of pharmacological treatments (i.e., tramadol, amitriptyline, fluoxetine, duloxetine, milnacipran, moclobemide, pirlindol, tropisetron, pramipexole, and pregabalin), a recommendation strength of “B” to aerobic exercise, and a recommendation strength of only “D” to cognitive behavioral therapy (CBT) ***(Bellato et al.,2012).***

Prolotherapy is an injection technique that treats ligamentous laxity by injecting an area of ligament or

tendon laxity with an irritant dextrose solution of concentration 12.5% that causes cells to lose water and reaches a point of injury response through osmotic gradient. This injury stimulates fibroblast proliferation through initiation of an inflammatory response to restore normal connective tissue strength in the area ***(Hassan et al., 2017).***

The word 'proli' is a Latin Word that means 'offspring';'proliferate'-toproliferate new cells ***(Hauser, 2011).***

There are many solutions used in prolotherapy as phenol, glycerin and recently platelets rich plasma (PRP). However, dextrose is the most commonly used solution in prolotherapy worldwide as it is water soluble and a normal blood chemistry component, thus it can be injected safely in large amounts ***(Hauser,2011).***

Good results were shown by prolotherapy in osteoarthritis, low back pain, sacroiliitis, and tendinopathies as tennis elbow ***(Rabago,2013).***

Prolotherapymight be apotentialline of treating refractory patients of FM, as it depends on injecting the tender points that are postulated to be the leading cause behind other disturbing symptoms of FM***(Hauser, 2011).***

It was suggested by Reeves in a study in 1994 for treating FM symptoms, yet no further attention was given by other studies since then, until re-suggested by Abd El Ghany and her colleagues in a study in 2018, in comparison to Transmagnetic cranial stimulation (rTMS), and proved good results.

Aim of the Study

To assess the potential role of prolotherapy in treating the most tender points of fibromyalgia patients as a trial to improve symptoms.

FIBROMYALGIA

Fibromyalgia (FM) is a chronic, non-inflammatory widespread pain disorder associated with a complex of symptoms as fatigue, depression, cognitive impairment. It is the second most common disease encountered in rheumatology practice. It is a persistent disorder that carries the potential of being debilitating to the patient through having a negative effect on the patient`s everyday activities, worsening the mood, impairing the relationships with the surrounding environment, affecting the capability to work and become productive, and thus imposing huge financial burdens on the society and on the patient herself ***(Berger et al., 2007).***

'Fibromyalgia' is the latest term for what was once called 'fibrositis` or 'pain syndrome' ***(Bellato et al., 2012).***

Fibromyalgia is nine times more common in females than males ***(Mas et al., 2008).*** It is thought that this attributes to the higher sensitivity of females to painful stimuli, with a higher pain threshold in men ***(Arnold, 2010).***

Etiology (theories) and pathogenesis:

The etiology of FM is still unclear, however, there have been several proposed theories for the disorder, including nervous (central and autonomic), endocrinal, and immune systems, triggered by genetic, metabolic, environmental and psychological factors ***(Bellato et al., 2012).***

Pain is a hallmark symptom in FM, and multiple theories try to explain its etiology ***(Aaron et al., 2003).***

Theories:

1) Nervous system:

Central Theories:

Several researches propose the neurogenic origin of the chronic widespread body ache - that is the main presentation of FM-. It is thought that FM arises from the hightened sensitization of the central nervous system to pain stimuli, also known as 'hyperalgesia', besides' allodynia'- which is the increased sensitivity to non-painful stimuli ***(Clauw, 2007).***

Hyperalgesia is believed by some authors to be attributed to the 'windup' phenomenon, which refers to the temporal summation of pain, or in other words, the elevated C-fibers evoked potentials in the dorsal horn due to their repititive stimulation ***(Burgmer et al., 2008).***

This mechanism is believed to be exacerbated by dysfunction of the descending spinal cord tracts which modulate our pain perception ***(Staud et al., 2002).***

It is believed that brain derived neurotrophic factor (BDNF), a member of neurotrophines and the most prevalent growth factor in central nervous system(CNS), is involved in CNS development and neuronal plasticity, and therefore is also involved in multiple psychiatric diseases. A recent study proved the elevation of BDNF level in serum of FM patients suffering from depression, compared to those with no depressive symptoms. Therefore, this

suggests that BDNF may be involved in FM pathogenesis ***(Fawzy et al.,2015).***

Multiple neurotransmitters have been linked to the etiology of FM. The most important of these, is the serotonin (5-HT), which plays a role in pain modulation, and whose metabolite –tryptophan- was found to be low in FM patients' blood and CSF ***(Wolfe,1997).***

High substance P levels, dopamine and endorphins may also be involved in FM development ***(Wood,2004).***

Autonomic Theory:

As regards the role of autonomic nervous system, sympathetic nervous system seems to be hyperactive in FM patients, together with hypersecretion of norepinehrine***(Stisi et al.,2008).***

2) ***Neuroendocrine system:*** Decreased 5-HT levels is thought to affect the hypothalamic-pituitary-adrenal axis, leading to increased cortisone levels, stress-induced decreased corticotropin-releasing hormone (CRH) levels, and thus elevated adrenocorticotrophic hormone (ACTH) levels ***(Bradley,2009).***

3) ***Immunesystem:*** Since glial cells are believed to participate in pain modulation, they release cytokines and reactive oxygen species (ROS),once activated by painful stimuli, to prolong the neurons` hyperexcitability***(Watkins et al.,2002).***

Another presented evidence for the immune system involvement theory is the association of FM with

autoimmune diseases, mainly rheumatoid arthritis (RA), Systemic lupus (SLE), and Sjogren syndrome, yet no specific autoantibodies have been linked to the diagnosis of secondary FM ***(Buskila et al., 2003).*** Some researchers suggested that FM development may precede autoimmune diseases classic symptoms appearance in some cases ***(Buskila,2009).***

- *Triggering factors:*

1. *Genetic factors:* Polygenetic factors are thought to be linked to the pathogenesis of FM, as the serotonin transporter genes, dopamine D4 receptor gene, and the HLA region ***(Buskila,2009; Woolf,2011).***

Pain is suggested to have a genetic background, through pain- related genes which affect the expression of protein products, thus affecting the pain pathway. Multiple genes play a role in pain sensitivity, including genes encoding voltage- gated sodium channels, and opioid receptors ***(Mogil,2012).***

2. Metabolic factors: One research observed an association between FM symptoms, especially chronic fatigue and mood disorders, with individuals with slow metabolism ***(Garrison and Breeding, 2003).***

3. Environmental factors: Different extrinsic trigger factors seem to be capable of inducing fibromyalgia, including chemicals,vaccinations, andinfections as HIV, HCV, Coxackie B, and parvovirus ***(Albrecht and Rice, 2016).***

Physical trauma, leading to weak or lax tendons, have been proposed as potential nociceptors in FM patients, because the fibromyalgia tender points were noticed to be over the sites of tendons` insertions in bone, which have low pain threshold ***(Reeves,1994).***

One of the researches demonstrated the high prevalence of FM syndrome with low socioeconomic class. This was attributed to the high load of manual work low-

income individuals are involved in, which makes them more susceptible to trauma ***(Assumpcao et al.,2009).***

4. Psychological factors: Multiple researchers have been interested in the impact of emotional traumas, as history of childhood abuse, on the development of FM symptoms ***(Albrecht and Rice, 2016).***

Clinical picture:

Fibromyalgia is a diffuse agonizing disorder, with a complex of associated systemic symptoms.Pain, fatigue and sleep disturbance are the hallmark symptoms of fibromyalgia ***(Aaron et al.,2003).***

Pain is usually the most disturbing complaint in fibromyalgia, it`s either 'regional', i.e. involves parts of the body; for example upper or lower arms, neck, legs or thighs; or 'localized' to classical points, known as 'tender points'. The pain is chronic, migratory, and the patient usually attributes its start to a certain physical or mental trauma.

Other common forms of pain include: irritable bowel syndrome, headache, epigastric pain, and chest pain ***(Boomershine,2011; Wolfe et al.,2011).***

Sleep disturbance associated with FM includes: sleep onset and sleep maintenance problems- with increased arousals-, a reduction of total sleeping hours or non-restorative, unrefreshingsleep***(Yi et al., 2006).***

Sleep maintenance disorders are more problematic to patients than sleep onset.

Hypothalamic pituitary axis disruption is believed to be the leading cause behind sleeping disorders.

Polysomnography in FM patients revealed decreased stage 4 slow wave sleep (deep sleep), and increased stage 1 of light sleep.

Despite extreme fatigue, FM patients start having negative thoughts regarding sleeping time, because they are always worried of having difficulty falling asleep. Furthermore, they keep tossing and turning in bed, with easy waking up in the middle of the night due to the least amount of noise, or due to urination frequency which is usually associated with the syndrome. Patients are unlikely to fall asleep after waking up, so this disturbed sleep can be described as 'blocks of sleep'. Poor sleep leads to fatigue in the morning, less interest in work and productivity, less concentration, together with more exacerbation in pain levels.

Other triggers of poor sleep quality include: drinking alcohol, anxiety, and nocturia***(Roizenblatt et al.,2011).***

Depression is one of the major signs observed in FM patients. Patients are constantly feeling down, with little desire in doing things, and it may even lead the patient to think about hurting themselves ***(Okifuji et al.,2000).***

Multiple studies have linked the development of FM and mood disorders to a common neurologic abnormality, which is a decline in the neurotransmitters, serotonin and norepinephrine, in the brain ***(Thieme et al.,2004).***

Other common symptoms of FM include: Cognitive disturbance, parasthesia, muscle stiffness, dizziness, nausea,vomiting, hearing difficulties, tinnitus, dry eyes, blurred vision, dry mouth, taste changes, rash, sun sensitivity, hair fall, diarrhea or constipation, painful urination, bladder spasms, nocturia, Raynaud`s phenomenon, wheezing, dyspnea, seizures, difficulty in sexuality, and appetite changes ***(Wolfe et al.,2011).***

Unfortunately,fibromyalgia leads to a number of complications:

1. Opioid and alcohol dependence***(Kim et al., 2013)***
2. Marked functional impairment, increased abseentism from work, and therefore increasing their financial burdens due to misdiagnosis, seeking help from multiple specialists,and the several costy investigations the patient is asked to do, for several years before the patient is correctly diagnosed ***(Macfarlane et al.,2017).***
3. Appetite changes, most commonly overeating, which leads to weight gain and therefore worsens the FM symptoms, especially sleep disturbance due to obstructive sleep apnea ***(Curto et al.,2017).***

Diagnosis:

Fibromyalgia diagnosis is merely clinical, with no detected markers to confirm its diagnosis. It was long considered a 'diagnosis of exclusion', where patients with chronic generalized body aches, not explained by any investigations, were diagnosed with FM ***(Sim,2008).***

Two types of FM are identified: Primary and secondary. The cause of primary FM is yet not fully known, but it may be triggered by infection, inflammation, stress, and trauma. Secondary FM is due to other diseases, as rheumatic diseases (as rheumatoid arthritis, spondylo-negativearthropathies, and systemic lupus erythromatosis), hypothyroidism and malignancy. In this type, treatment of the primary disease improves the FM symptoms ***(Wallace et al.,2001).***

Laboratory investigations to be cleared before diagnosis of FM are; thyroid function tests (TFTs), liver function tests (LFTs), kidney function tests (KFTs), ESR, CRP, ANA and Anti-CCP.

Furthermore, in 1990, the American College of Rheumatology (ACR) developed new criteria for the diagnosis of fibromyalgia, which raised the awareness regarding this syndrome ***(Wolfe et al.,1990).***

The ACR 1990 criteria consists of two major criteria, as follows:

a. A history of widespread pain - bilateral, above and below the waist, axial as well as peripheral- present for 3 months or more.

b. Tenderness in no less than 11 of 18 defined tender points - also known as 'pressure points'.

Tender points are 18 specific points in the body, over the tendons` insertions in bones, that are painful-not just irritating- on exerting a pressure equivalent to 4 kg/cm^2 (till the thumb nail bed blanches).