ISSN: 2230-9926

*Available online at http://www.journalijdr.com*

IJDR

*International Journal of Development Research*
*Vol. 09, Issue, 06, pp.28250-28261, June 2019*

RESEARCH ARTICLE OPEN ACCESS

# FIBROMYALGIA SYNDROME AMONG PATIENTS WITH HYPOTHYROIDISM IN MOSUL

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**ARTICLE INFO**

***Article History:***

Received 27th March, 2019
Received in revised form
15th April, 2019
Accepted 10th May, 2019
Published online 30th June, 2019

***Key Words:***

Levothyroxin,
Fibromyalgia,
Hypothyroidism.

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**ABSTRACT**

**Objective:** To study the relationship between fibromyalgia syndrome and hypothyroidism patients in Mosul city. **Patients and methods:** A case –control study design was adopted .The two stages classification process proposed by 1990 American College of Rheumatology multicenter criteria committee of FMS was applied as an objective assessment of hypothyroidism patient and control group about full history, complete clinical examination and thyroid hormone analysis. **Stage I:** A pain questionnaire was given a sample of 124 (74 female and 50 male) consecutive patients with hypothyroidism mean age 24.8 years (range 16-60 years) who were attending thyroid clinic in Oncology and Nuclear Hospital in Mosul. **Stage II:** All patients with chronic wide spread pain were examined by same examiner for 18 binder points. Another 124 healthy individuals matched for age and sex were examined as controls. **Results:** Chronic wide spread pain was present in 42 of 124 (33.9%) hypothyroidism patients compared to only 29 (23.4%) individual in the control group (P=0.0001). Fibromyalgia syndrome was present in 22 of 124 (17.7%) hypothyroidism patients are compared to only 5 (4%) individuals in the control group( OR = 5.13 ,P=0.001). Female patients with hypothyroidism have high percentage of chronic wide spread pain and fibromyalgia syndrome compared to male patients in the study group. There were positive correlation between fibromyalgia syndrome and hypothyroidism patients with regard to duration of hypothyroidism of more than five years (P=0.0008) but no significant relation with dose of Levothyroxine, age and Body Mass Index **Conclusion:** Chronic wide spread pain and fibromyalgia syndrome are positively associated with hypothyroidism. fibromyalgia syndrome is more common in female who had disease duration ≥ 5 and within middle age. No role of Levothyroxin in the present study.



**Citation: Sahar Salim AL-Taie, Muna Saud Ahmed and Saad Ali ALgiburi. 2019.** "Fibromyalgia Syndrome among Patients with Hypothyroidism in mosul.", *International Journal of Development Research*, 09, (06), 28250-28261.

## INTRODUCTION

Fibromyalgia (FM or FMS) is characterised by chronic widespread pain and allodynia (a heightened and painful response to pressure) (Ngian, 2011). Its exact cause is unknown but is believed to involve psychological, genetic, neurobiological and environmental factors (Maletic, 2009). Fibromyalgia symptoms are not restricted to pain, leading to the use of the alternative term fibromyalgia syndrome for the condition. Other symptoms include debilitating fatigue, sleep disturbance, and joint stiffness. Some patients also report difficulty with swallowing, bowel and bladder abnormalities. Fibromyalgia is frequently comorbid with psychiatric conditions such as depression, anxiety and stress-related disorders such as post traumatic stress disorder. Not all fibromyalgia patients experience all associated symptoms (Ngian, 2011).

Fibromyalgia is estimated to affect 2–4% of the population, with a female to male incidence ratio of approximately 9:1[(3)]. The term "fibromyalgia" derives from new Latin, *fibro-*, meaning "fibrous tissues", Greek *myo-*, "muscle", and Greek *algos-*, "pain"; Fibromyalgia has been recognized as a diagnosable disorder by the US National Institutes of Health and the American College of Rheumatology[(2)]. FMS is defined as primary when there are no other coexisting diseases and secondary _ concomitant when it coexists with another disorder (Maletic, 2009). Fibromyalgia is a central nervous system disorder, is described as a "central sensitization syndrome" caused by neurobiological abnormalities which act to produce physiological pain and cognitive impairments as well as neuro-psychological symptomatology (Ngian, 2011). Rheumatologists, neurologists, and pain specialists tend to view fibromyalgia as a pathology of both biological and neurobiological origin (Maletic, 2009).

**Classification:** Fibromyalgia is classified as a disorder of pain processing due to abnormalities in how pain signals are processed in the central nervous system (Wolfe, 1989). The American College of Rheumatology classify fibromyalgia as being a functional somatic syndrome (Maletic, 2009). The expert committee the European League Against Rheumatism classify fibromyalgia as a neurobiological disorder and as a result exclusively give pharmaco-therapy their highest level of support (Wolfe, 1989). The International Classification of Diseases (ICD-10) lists fibromyalgia as a diagnosable disease under "Diseases of the musculoskeletal system and connective tissue" and states that fibromyalgia syndrome should be classified as a functional somatic syndrome rather than a mental disorder. Although mental disorders and some physical disorders commonly are co-morbid with fibromyalgia-especially anxiety, depression and irritable bowel syndrome and chronic fatigue syndrome - the ICD states that these should be diagnosed separately (Maletic, 2009).

**Signs and symptoms:** The defining symptoms of fibromyalgia are chronic widespread pain, fatigue, and heightened pain in response to tactile pressure (allodynia). Other symptoms may include tingling of the skin, prolonged muscle spasms, weakness in the limbs, nerve pain, muscle twitching, palpitations (Wolfe, 1989), functional bowel disturbances, and chronic sleep disturbances (Sommer, 2012). Many patients experience cognitive dysfunction (known as "fibrofog"), which may be characterized by impaired concentration, problems with short and long-term memory, short-term memory consolidation, impaired speed of performance, inability to multi-task, cognitive overload, and diminished attention span. Fibromyalgia is often associated with anxiety and depressive symptoms (Sommer, 2012). Chronic myofascial pain, diffuse non-dermatomal paresthesias, functional bowel disturbances and irritable bowel syndrome, genitourinary symptoms and interstitial cystitis, dermatological disorders, headaches, myoclonic twitches, and symptomatic hypoglycemia. Although fibromyalgia is classified based on the presence of chronic widespread pain, pain may also be localized in areas such as the shoulders, neck, low back, hips, or other areas. Many sufferers also experience varying degrees of myofascial pain and have high rates of comorbid temporomandibular joint dysfunction (Wallace, 2002).

**Causes**: The cause of fibromyalgia is unknown. however, several hypotheses have been developed including "central sensitization". This theory proposes that fibromyalgia patients have a lower threshold for pain because of increased reactivity of pain-sensitive nerve cells in the spinal cord or brain (White, 1999). Neuropathic pain and major depressive disorder often co-occur with fibromyalgia – the reason for this comorbidity appears to be due to shared genetic abnormalities, which leads to impairments in monoaminergic, glutamatergic, neurotrophic, opioid and proinflammatory cytokine signaling. In these vulnerable individuals psychological stress or illness can cause abnormalities in inflammatory and stress pathways which regulate mood and pain. Eventually a sensitisation and kindling effect occurs in certain neurones leading to the establishment of fibromyalgia and sometimes a mood disorder (Buskila, 1993). The evidence suggests that the pain in fibromyalgia results primarily from pain processing pathways functioning abnormally. In simple terms it can be described as the volume of the neurones being set too high and this hyper-excitability of pain processing pathways and under-activity of inhibitory pain pathways in the brain results in the affected individual experiencing pain. Some of the neurochemical abnormalities that occur in fibromyalgia also regulate mood, sleep and energy, this explaining why mood, sleep and fatigue problems are commonly co-morbid with fibromyalgia (Clauw, 1997).

**Epidemiology:** Fibromyalgia is seen in about 2% of the general population and affects more females than males, with a ratio of 9:1 by ACR criteria. ( Maletic, 2009) It is most commonly diagnosed in individuals between the ages of 20 and 50. Although onset can occur in childhood (Wolfe, 1997).

**Diseases associated with fibromyalgia or, at least in part, may show some similar symptoms (Bennett):**

**Rheumatic diseases**

Lupus erythematosus
Rheumatoid Arthritis
Sjögren syndrome
Polymyositis
Polymyalgia rheumatica
Osteomalacia
Hypermobility syndromes
Regional Pain Syndromes

**Neurologic Diseases**

Carpal tunnel syndrome
Cervical radiculopathy
Multiple Sclerosis
Myopathies (dystrophies, metabolic, drug-as statin .

**Endocrine diseases**

Hypothyroidism
Noninsulin Diabetes mellitus
Hyperparathyroidism

**Neoplasms**

Multiple Myeloma
Metastasis (breast, lung, prostate)

**Tapering of steroid.**

**Infections (Hepititis C)**

**Pathophysiology**

Dopamine dysfunction: The "dopamine hypothesis of fibromyalgia" proposes that the central abnormality responsible for symptoms associated with fibromyalgia is a disruption of normal dopamine-related neurotransmission (Simms, 1988). Insufficient dopamine in a part of the body is termed hypodopaminergia. Dopamine is a catecholamine neurotransmitter with roles in pain perception and natural analgesia. There is also strong evidence for a role of dopamine in restless leg syndrome which is a condition found frequently in patients with fibromyalgia. Some fibromyalgia patients responded in controlled trials to pramipexole, a dopamine agonist that selectively stimulates dopamine D2/D3 receptors and is used to treat both Parkinson's disease and restless leg syndrome (Sommer, 2012).

**Serotonin metabolism:** In 1975, researchers hypothesized that serotonin, a neurotransmitter that regulates sleep patterns, mood, concentration and pain, could be involved in the pathophysiology of fibromyalgia-associated symptoms. In 1992, decreased serotonin metabolites in patient samples and cerebrospinal fluid were reported (Glass, 2006). However, selective serotonin reuptake inhibitors (SSRIs) have met with limited success in alleviating the symptoms of the disorder, while drugs with activity as mixed serotonin-norepinephrine re-uptake inhibitors (SNRIs) have been more successful. However, the relevance of dysregulated serotonin metabolism to pathophysiology is a matter of debate (Buskila, 1993). Complicating the analysis, one of the more effective types of medication for the treatment of the disorder (i.e. serotonin 5-HT3 antagonists) actually blocks some of the effects of serotonin (Pettersson, 1995).

**Growth hormone:** Levels of hormones under the direct or indirect control of growth hormone (GH), including IGF-1, cortisol, leptin and neuropeptide Y may be abnormal in people with fibromyalgia but supplementing growth hormone in patients does not have large effects, and a 2007 literature review reported a need for "further study before any solid recommendations can be made (Buskila, 2007).

**Poly-modal sensitivity:-**Results from studies examining responses to experimental stimulation suggest that fibromyalgia patients may have heightened sensitivity of the nociceptive system, which senses pressure, heat, cold, electrical and chemical stimulation. Experiments examining pain regulatory systems have shown that fibromyalgia patients display an exaggerated wind-up in response to repetitive stimulation and an absence of exercise-induced analgesic response (Schweinhardt, 2008).

**Neuroendocrine disruption:** Patients with fibromyalgia may have alterations of normal neuroendocrine function, characterized by mild hypocortisolemia, hyperreactivity of pituitary adrenocorticotropin hormone release in response to challenge, and glucocorticoid feedback resistance. Low insulin-like growth factor 1 (IGF-1) levels in some fibromyalgia patients have led to the theory that these patients may actually have a different, treatable syndrome, adult growth hormone deficiency (Mountz, 1995). Other abnormalities include reduced responsivity of thyrotropin and thyroid hormones to thyroid-releasing hormone, a mild elevation of prolactin levels with disinhibition of prolactin release in response to challenge and hyposecretion of adrenal androgens[(7)].These changes might result from chronic stress, that, after being perceived and processed by the central nervous system, activates hypothalamic corticotrophin-releasing hormone neurons. Chronic overactivity of these neurons could disrupt normal function of the pituitary-adrenal axis and cause an increased stimulation of hypothalamic somatostatin secretion, which, in turn, could inhibit the secretion of other hormones (White, 1999).

**Sympathetic hyperactivity:-** Functional analysis of the autonomic system in patients with fibromyalgia has demonstrated disturbed activity characterized by hyperactivity of the sympathetic nervous system at baseline with reduced sympathoadrenal reactivity in response to a variety of stressors including physical exertion and mental stress. Fibromyalgia patients demonstrate lower heart rate variability, an index of sympathetic/parasympathetic balance, indicating sustained sympathetic hyperactivity, especially at night (Clauw, 1997). In addition, plasma levels of neuropeptide Y, which is co-localized with norepinephrine in the sympathetic nervous system, have been reported as low in patients with fibromyalgia, while circulating levels of epinephrine and norepinephrine have been variously reported as low, normal and high. Administration of interleukin-6, a cytokine capable of stimulating the release of hypothalamic corticotropin-releasing hormone which in turn stimulates activity within the sympathetic nervous system, results in a dramatic increase in circulating norepinephrine levels and a significantly greater increase in heart rate over baseline in fibromyalgia patients as compared to healthy controls (Demitrack, 1998).

**Cerebrospinal fluid abnormalities:-** One of the most reproduced laboratory finding in patients with fibromyalgia is an elevation in cerebrospinal fluid levels of substance P, a putative nociceptive neurotransmitter (Yunus, 1983). Metabolites for the monoamine neurotransmitters serotonin, norepinephrine, and dopamine—all of which play a role in natural analgesia—have been shown to be lower, while concentrations of endogenous opioids (i.e., endorphins and enkephalins) appear to be higher. The mean concentration of nerve growth factor, a substance known to participate in structural and functional plasticity of nociceptive pathways within the dorsal root ganglia and spinal cord, is elevated. There is also evidence for increased excitatory amino acid release within cerebrospinal fluid, with a correlation demonstrated between levels for metabolites of glutamate and nitric oxide and clinical indices of pain (Iadarola, 1995).

**Brain imaging studies:-**Evidence of abnormal brain involvement in fibromyalgia has been provided via functional neuroimaging. The first findings reported were decreased blood flow within the thalamus and elements of the basal ganglia and mid-brain (i.e., pontine nucleus) (Bartels, 2009).

**Diagnosis:** There is no single test that can fully diagnose fibromyalgia and there is debate over what should be considered essential diagnostic criteria and whether an objective diagnosis is possible[(22)] . In most cases, patients with fibromyalgia symptoms may also have laboratory test results that appear normal and many of their symptoms may mimic those of other rheumatic conditions such as arthritis or osteoporosis. In general, most doctors diagnose patients with a process called differential diagnosis, which means that doctors consider all of the possible things that might be wrong with the patient based on the patient's symptoms, gender, age, geographic location, medical history and other factors. They then narrow down the diagnosis to the most likely one. The most widely accepted set of classification criteria for research purposes was elaborated in 1990 by the Multicenter Criteria Committee of the American College of Rheumatology (Wolfe, 1990). These criteria, which are known informally as "the ACR 1990", define fibromyalgia according to the presence of the following criteria:

- A history of widespread pain lasting more than three months—affecting all four quadrants of the body, i.e., both sides, and above and below the waist.
- Tender points—there are 18 designated possible tender points (although a person with the disorder may feel pain in other areas as well). Diagnosis is no longer based on the number of tender points (Buskila, 2006).

The ACR criteria for classification of patients were originally established as inclusion criteria for research purposes and were not intended for clinical diagnosis but have now become the *de facto* diagnostic criteria in the clinical setting. It should be noted that the number of tender points that may be active at any one time may vary with time and circumstance. A controversial study done by a legal team looking to prove their client's disability based primarily on tender points and their widespread presence in non-litigious communities prompted the lead author of the ACR criteria to now question the useful validity of tender points in diagnosis (Clauw, 2011). Use of control points has been used to cast doubt on whether a person has fibromyalgia, and to claim the person is malingering, however, no research has been done for the use of control points to diagnose fibromyalgia and such diagnostic tests have been advised against and that patients complaining of pain all over should still have fibromyalgia considered as a diagnosis (Maletic, 2009). Since the ACR criteria were originally published, research with mechanical devices that exert defined pressure indicate that diagnosis of fibromyalgia cannot be done objectively by machine and require a physician's subjective estimate of how much pressure should be exerted. Fibromyalgia is widely under-diagnosed with up to 75 percent of people suffering with fibromyalgia not being diagnosed (Clauw, 2011).

**Management:** As with many other medically unexplained syndromes, there is no universally accepted treatment or cure for fibromyalgia, and treatment typically consists of symptom management. Developments in the understanding of the pathophysiology of the disorder have lead to improvements in treatment, which include prescription medication, behavioral intervention and exercise. Indeed, integrated treatment plans that incorporate medication, patient education, aerobic exercise and cognitive-behavioral therapy have been shown to be effective in alleviating pain and other fibromyalgia-related symptoms (Mannerkorpi, 2000). The Association of the Scientific Medical Societies in Germany, the European League Against Rheumatism and the Canadian Pain Society[11] currently publish guidelines for the diagnosis and management of FMS.

**Psychological therapies:** Cognitive behavioral therapy (CBT) and related psychological / behavioral therapies are treatments which have been shown to have a small to moderate effect in reducing symptoms of fibromyalgia in randomized controlled trials. The greatest benefit occurs when CBT is used along with exercise (Cook, 2004).

**Antidepressants:** Antidepressants are "associated with improvements in pain, depression, fatigue, sleep disturbances, and health-related quality of life in patients with FMS" (Cook, 2004). The goal of antidepressants should be symptom reduction and if used long term, their effects should be evaluated against side effects. A small number of people benefit significantly from duloxetine and milnacipran and the tricyclic antidepressants (such as amitriptyline) however many people experience more adverse effects than benefits (Donaldson, 2003).

**Anti-seizure medication:-** The anti-convulsant drugs gabapentin and pregabalin may be used. Gabapentin is of a significant benefit in about 30% of people who take it however is commonly associated with adverse effects. A Cochrane review of pregabalin use in chronic pain concluded that "A minority of patients will have substantial benefit with pregabalin, and more will have moderate benefit. Many will have no or trivial benefit, or will discontinue because of adverse events. A meta-analysis of four trials of pregabalin in fibromyalgia found that, for people who did respond to pregabalin, there was a reduction in their time off work of greater than 1 day per week (Michiels, 1998).

**Opioids:** The Association of the Scientific Medical Societies in Germany makes no recommendation either for or against the use of weak opioids because of the limited amount of scientific research addressing their use in the treatment of FM. They strongly advise against using strong opioids. The European League Against Rheumatism recommends the weak opioid such as tramadol but not strong opioids. The Canadian Pain Society says that , starting with a weak opioid like tramadol, can be tried but only for patients with moderate to severe pain that is not well-controlled by non-opioid pain-killers. They discourage the use of strong opioids, and only recommend using them while they continue to provide improved pain and functioning. Healthcare providers must monitor patients on opioids for ongoing effectiveness, side effects and possible unwanted drug behaviours[30]. The combination of tramadol and paracetemol has demonstrated efficacy, safety and tolerability (for up to two years in the management of other pain conditions) without the development of tolerance. It is as effective as a combination of codeine (another mild opioid) and paracetamol but produces less sleepiness and constipation (Janda, 1988).

**Exercise:** Exercise improves fitness, sleep and may reduce pain and fatigue in some people with fibromyalgia. In particular, there is strong evidence that cardiovascular exercise is effective for some patients. Long-term aquatic-based exercise has been proven beneficial as it combines cardiovascular exercise with resistance training (Clark, 2001). However, due to the cold sensitivities of people with fibromyalgia syndrome, aquatic therapy must take place in a warm pool. Not only that, but the air temperature outside of the pool must also be heated to prevent fibromyalgia patients from getting chills and aches when out of the water. This involves a specialised pool facility, which makes this therapy more expensive and less accessible than regular swimming exercise (Clark, 2001).

**Prognosis:** Although FMS neither degenerative nor fatal, the chronic pain of fibromyalgia is pervasive and persistent. Most fibromyalgia patients report that their symptoms do not improve over time. An evaluation of 332 consecutive new fibromyalgia patients found that disease-related factors such as pain and psychological factors such as work status, helplessness, education, and coping ability had an independent and significant relationship to FM symptom severity and function (Karjalainen, 2000).

**Hypothyroidism:** Hypothyroidism, like many chronic conditions, is associated with long-term morbidity that can be minimized through careful management[34,35]. Primary thyroid failure is a continuous progression from a relatively symptom-free stage into overt disease in which abnormal levels of thyroid hormones are accompanied by troubling symptoms, cognitive impairment, and a heightened risk of cardiovascular morbidity (Dugbarty, 1998). There is ongoing debate over what constitutes “normal” levels of thyroid hormones. As a result, researchers are exploring the risks posed by subclinical,

asymptomatic disease, with the goal of clarifying the indications for treatment (Dugbarty, 1998). The fundamental effective pharmacologic treatment-replacement of thyroid hormones has not changed in decades (Brent, 2011). The basic approach to management encompasses educating the patient about the disease and treatment; ensuring medication adherence; titrating dosage to assure clinical well-being; and monitoring treatment response. Nonetheless, under and over-treatment are common (Okosieme, 2011). Pharmacists are well positioned to correct this therapeutic inadequacy by identifying and correcting common reasons that affect drug availability, such as drug interactions (Dugbarty, 1998), effects of common co morbid conditions, [Okosieme, 2011] timing of administration and assuring drug formulation consistency. Pharmacists can make a dramatic difference in treatment success by educating the patient and monitoring adherence (Brent, 2011).

**Normal Thyroid Function:-**The thyroid is an endocrine gland consisting of 2 lobes connected by the isthmus (Jameson, 2009). It is located in the throat just beneath the larynx. Activation of the thyroid by thyroid-stimulating hormone (TSH or thyrotropin) leads to the production of thyroxine (T4), which is metabolized to a highly active form, triiodothyronine (T3) (Wartofsky, 2005). The normal thyroid gland produces about 80% T4 and about 20% T3; however, T3 possesses about 4 times the hormone "strength" of T4. Production of the 2 thyroid hormones is regulated via a classic endocrine feedback loop. Low levels of T3 and T4 stimulate the release of thyrotropin- releasing hormone (TRH) in the hypothalamus. TRH, in turn, stimulates production of TSH in the pituitary gland. TSH, which is released rapidly with increased TRH, determines the normal physiologic set point for thyroid hormone levels. Thyroid hormones are essential for normal metabolic functioning. In children, these hormones are crucial determinants of normal development, especially of the central nervous system and bone (AACE, 2002). Absence of thyroid hormone in neonates can lead to irreversible mental retardation and is associated with widespread brain abnormalities (AACE, 2002). In adults, thyroid hormones maintain metabolic homeostasis by affecting the function of almost all organ systems. Thyroid function helps regulate breathing, heart and nervous system functions, body temperature, muscle strength, skin dryness, menstrual cycles, weight, and cholesterol levels (Wiersinga, 2001).

**Definition and Prevalence**:-The National Health and Nutrition Examination Survey (NHANES) III reports that hypothyroidism affects 3.7% of the United States population[41]. The mean age at diagnosis is 60 years, and the risk increases with age. The risk is 5-fold greater in persons aged ≥80 years compared with those aged 12 to 49 years. The incidence is 4 times greater in women than in men (Hennessey, 2010). Hypothyroidism is characterized by abnormally elevated TSH levels resulting from activation of the thyroid feedback loop to compensate for low levels of thyroid hormones T4 and T3 (Hennessey, 2010). TSH levels are monitored to deter-mine the severity of disease and the effects of treatment. The definition of an abnormal TSH level is controversial, and no absolute distinction between normal and abnormal is established (Tagami, 2010). Nonetheless, >95% of persons with-out thyroid disease have TSH levels <2.5 mIU/L, and the mean normal appears to be between 1.18 and 1.40 mIU/L.5 Levels >2.5 mIU/L warrant careful assessment of the patient's thyroid status (Mechanick, 2008).

Common Primary and Secondary Causes of Hypothyroidism (Bahn Chair, 2011)

- Primary
- Chronic autoimmune thyroiditis (Hashimoto's disease)
- Surgical removal of the thyroid gland
- Thyroid gland ablation with radioactive iodine
- External irradiation .
- Biosynthetic defect in iodine organification
- Replacement of the thyroid gland by tumor (lymphoma)
- Drugs (eg, lithium, interferon, amiodarone) Secondary
- Pituitary and hypothalamic disease

**Clinical Hypothyroidism:-** Clinical hypothyroidism is manifested by a wide range of nonspecific signs and symptoms, these usually become apparent at a TSH level >10 mIU/L.4 Symptoms are related to duration and severity of hypothyroidism and psychological characteristics of the patient (Stagnaro-Green, 2011). Associated morbidity includes impairment across cognetive domains such as general intelligence, complex attention and concentration, memory, perceptual and visuospatial function, ability to use language, and executive functions (Hollowell, 2012). Severe untreated hypothyroidism can lead to myxedema coma, an uncommon life-threatening condition. In neonates, hypothyroidism causes feeding problems, failure to thrive, constipation, sleepiness, and, if untreated, mental retardation. Affected children may experience impairment of linear growth and bone maturation (Kubota, 2010). Changes in the cardiovascular system are a prominent feature of hypothyroidism. The condition is characterized by bradycardia, pericardial effusion, increased peripheral vascular resistance, decreased pulse pressure, elevation of mean arterial pressure, and, in its most extreme form, heart failure. Dyslipidemia is common, as evidenced by increased levels of total and low-density lipoprotein cholesterol. In fact, the mean cholesterol level may be 50% above nor-mal. According to a recent Chinese survey, the dyslipidemia associated with elevated TSH may reflect a heightened risk of other components of metabolic syndrome, such as overweight/obesity, hyperglycemia, and hypertension (Kubota, 2010). Signs and symptoms of hypothyroidism in descending order of frequency (Vanderpump, 2002).

**Symptoms**

- Tiredness,
- weakness
- Feeling cold
- Hair loss.
- Difficulty concentrating and poor memory
- Constipation
- Weight gain with poor appetite
- Dyspnea
- Hoarse voice
- Menorrhagia (later oligomenorrhea or amenorrhea)
- Paresthesia
- Impaired hearing

**Signs**

- Dry coarse skin; cool peripheral extremities
- Puffy face, hands, and feet (myxedema)
- Diffuse alopecia

- Bradycardia
- Peripheral edema
- Delayed tendon reflex relaxation
- Carpal tunnel syndrome
- Serous cavity effusions

**Subclinical Hypothyroidism:-**In its subclinical form, hypothyroidism symptoms are minimal or absent but serum TSH levels are elevated in the presence of normal levels of free T4 and free T3[50]. Subclinical hypothyroidism is more prevalent than overt disease, affecting 4.3% to 9% of the general population. It is diagnosed in ≤20% of persons aged >60 years and is more common in women and persons with greater dietary iodine intake [Fentiman, 1985]. Some patients revert to a euthyroid state, while others progress to overt disease. The risk of progression is highest in those with TSH >2.0 mIU/L, women, the elderly, and persons with thyroid peroxidase antibodies [Fentiman, 1985] In some persons, subclinical hypothyroidism is manifested by subtle findings (alterations in lipid metabolism; or cardiac, gastrointestinal, neuropsychiatric, and reproductive abnormalities) or goiter. The connection between subclinical hypothyroidism and heightened cardiovascular risk is contentious, although there is a preliminary indication of an association with hyperlipidemia, arterial hypertension, and cardiovascular disease (CVD), as well as serum C-reactive protein and retinol binding protein 4 levels. Evidence to date suggests a continuum in the cardiac changes associated with subclinical disease through hypothyroidism (Sawin, 1985).

**Treatment indications and benefits:-** Hormone replacement therapy is indicated for all patients with clinical hypothyroidism. The goals of therapy are to normalize TSH concentrations (or T4 levels in secondary hypothyroidism) and improve clinical well- being. Optimizing thyroid hormone replacement is associated with reversing the dyslipidemia associated with hypothyroidism (Vanderpump, 1995). Treatment also has been associated with improvements in some aspects of cognitive functioning after 3 months (Centanni, 2006). Just as the definition of normal TSH levels has been debated, so has the goal of levothyroxine therapy. Because >95% of persons without thyroid disease have TSH levels <2.5 mIU/L, that would appear to be a reasonable upper limit. However, some experts recommend limiting it to <2 mIU/L.21 An arbitrary lower level of 0.4 mIU/L has been recommended; much lower levels are not advised because they are associated with risk of atrial fibrillation and boneloss[53]. Patients who have had thyroid cancer usually are taking higher doses of thyroxine and their target TSH level is lower than normal. The decision to treat subclinical hypothyroidism is controversial, since most patients are asymptomatic and many revert to normal thyroid status (Centanni, 2006). The American Association of Clinical Endocrinologists (AACE) recommends treatment when TSH levels exceed 10 mIU/L and when TSH levels are between 5 and 10 mIU/L in a patient with goiter or positive antithyroxidase antibodies [Vanderpump, 1995]. Others suggest that it may be reasonable to treat those with cardiovascular risk factors, pregnant women, and women with ovulatory dysfunction and infertility because there is some evidence of benefit [Walker, 1986] Studies of the effects of hormone replacement therapy on cardiovascular morbidity and mortality have yielded contradictory results in patients with subclinical hypothyroidism. Middle-aged patients appear to derive greater benefit than elderly patients (Walker, 1986).

**Levothyroxine:** Levothyroxine is metabolized to the more biologically active T3 in target tissues[55]. It has good oral bioavailability; between 70% and 80% of an administered dose is absorbed mostly in the stomach and small intestine. The peak serum concentration is reached in 2 to 4 hours and the half-life is 190 hours. It is available as tablets, gel capsules, and a lyophilized powder for injection (Desai, 2006). Levothyroxine can be administered once daily, preferably in a fasting state, because absorption is reduced by concurrent ingestion of food. In general, manifacturers recommend taking levothyroxine first thing in the morning with water 30 minutes before eating breakfast (Klein, 1980). Alternatively, patients may take the medication at bed-time A fatty meal reduces absorption by 40%. other foods to be avoided close to ingestion include coffee, fruit juices, milk, and soy products. Because levothyroxine has a narrow therapeutic window, accurate dosing is critical. Dosing should be based on the patient's lean body weight and tailored to the individual patient (Stockigt, 2001). The mean replacement dose is 1.6 µg/kg of body weight per day, which translates into 100 to 125 µg/d for a person who weighs 60 to 75 kg. Treatment generally may be initiated at the full replacement dose in young, healthy patients. In the elderly (aged >60 years) or in cardiac patients, in whom there is a theoretical risk of treatment-induced cardiac ischemia, initiating therapy in a lower daily dose (12.5-50.0µg) is appropriate. Dosage reassessment and titration are often required, and the maintenance dose may vary between 75 and 250µg. Factors such as age, weight, pregnancy status, medications, and co morbid conditions affect dosing requirements (Hamilton, 2008). Larger doses may be needed for infants and children, premenopausal women, and those with primary autoimmune hypothyroidism. Conversely, thyroxin requirements decline with advancing age due to reduced thyroid hormone metabolism. The test of choice for monitoring treatment efficacy in primary hypothyroidism is TSH level while in secondary or tertiary hypothyroidism, it is free T4 levels. Follow-up monitoring to determine the new steady- state concentration should occur no more than 6 weeks after thyroid replacement is initiated or adjusted because of the drug's prolonged half-life. Once a stable maintenance dose is established based on clinical response and TSH levels, annual evaluation generally is adequate (Grozinsky-Glasberg, 2006).

**Aims of the study**: The aim of this study is to study the relationship between fibromyalgia syndrome and hypothyroidism patients.

**Specific objective**

- To establish the frequency of F.M.S among hypothyroidism
- To describe the main clinical presentation of the study.
- To study the effect of age, gender, duration of hypothyroidism, BMI and dose Levothyroxin in fibromyalgia syndrome .

## PATIENTS AND METHODS

- **Study design:** A case control study design were be carried out in order to achieve the objective of present study at Mosul Thyroid Disease Clinic.
- **Study setting:** The present study were be conducted in Thyroid Clinic, Hospital of Oncology and Nuclear Medicine in Mosul city which is located at the right bank of Tigris river.

- **Study period:** The study will be conducted from 1/10/2012 to 1/5/2013.
- **Study sample:** The present study were include 124 hypothyroid patients diagnosed in Thyroid Clinic by physician based on full history, complete clinical examination and thyroid hormone analysis. Another 124 healthy individuals matched for age and sex will be collected from relative and accompanying persons of the patient attending to Thyroid Clinic will study as a control group.

**Exclusion criteria**

**Patients were excluded from the study if they had**

- Conditions mimic FMS (Bennett, 1997).
- Uncontrolled hypothyroidism.

**Administrative agreements:-**The official administrative agreement will obtained from DOH in Mosul before conducting this study. A signed consent was taken from all individuals studied.

**Data collection tools:** The questionnaire of the present study will contain information about patient's name, date, age, sex, consent, occupation, Wt, Ht. fibromialgia features [Appendix 1] (wide spread pain, tender point) associated feature (sleep disturbance, headache, fatigue, anxiety, depression, numbness, irritable bowel). Hypothyroidism: duration, TSH, control and uncontrolled. Levothyroxine dose. [Appendix 2 ]

**Statistical tests:** Statistical analysis was done using statistical package for social science software (SPSS16) for Windows. Association between different categorical variables was measured using Chi-square test or Fisher's exact test and where appropriate.The 95% confidence interval (CI) for odds ratio (OR) was calculated. P-values<0.05 were considered significant.

**Outcome measures:-**Association between F.M.S and hypothyroidism

## RESULTS

Table (1) shows the demographic distribution of both Hypothyroidism patients and controls. There were 124 patients with Hypothyroidism, female 74 (59.7%), and male 50 (40.3%).One hundred twenty four healthy controls, 70 female (56.5%) and 54 male (43.5%). The mean age for Hypothyroidism patients and controls was 42.5 year both groups . Table (2) shows most of hypothyroidism patients and individuals in the control group had normal body mass index (BMI) 75 (60.5 %) and 70 (56.5 %) respectively while the rest were over weight or obese. Table (3) shows FMS was reported in 22 (17.7%) patients in hypothyroidism group compared to 5 (4%) individuals in the control group (P= 0.001). Table (4) There were high proportion female with hypothyroidism 19 (25.7%) having FMS compared to male patients 3 (6%) .Their mean age was 42.5 ( range 13-60 year ). There were high proportion with hypothyroidism having FMS above age of ≥40 years 15 (20%), compared to 7 (14.3%) <40 years with no significant statistical differences P = 0.566. \There were no significant statistical differences in the distribution of FMS among hypothyroidism patient below and above body mass index (BMI) 25 Kg\m$^2$. Table (5) shows hypothyroidism patients with FMS had a mean disease duration of 6 years (2-10) the least disease duration was 2 years, hypothyroidism patients with disease duration ≥ 5 years were more prone to have FMS with significant statistic relationship (P = 0.0008). The mean relapse periods in patients with hypothyroidism were 2 per day (range 1-3) , the least number of relapse period was 1 year , FMS more prone in hypothyroidism patients having repeated relapse period with significant statistical differences (P = 0.016). There were no significant statistical differences in the distribution of FMS among hypothyroidism patients receiving Levothyroxin below and above 50mg\day. Table (6) shows CWP was reported in 42 (33.9%) patients in hypothyroidism group compared to 35(28.2%) individuals in the control group (P=0.0001).

## DISCUSSION

The classification and treatment of FMS symptoms complex are controversial matters, not only with in and among the medical specially societies but also among patients and their families (Hauser, 2009). Many rheumatologists, neurologists and pain specialist, as well as many patients, consider FMS to be a distinct illness associated with pathological changes in the muscles and connective tissue and with characteristic functional abnormalities of the CNS (Hauser, 2009).

In this study the prevalence rate of FMS among hypothyroidism patients was reported in 17.7% of the sample studied, an association which is the best our knowledge not previously reported in our locality, FMS was recorded in association with many other medical illness, this result showed that FMS was repeated in association with hypothyroidism less frequently than with what was noted in some other medical diseases. FMS was reported in 25% of patients with rheumatoid arthritis (Wolfe, 1984), and hemophilia A (Ma'youf, 2010), 50% of patients with sjogren syndrome[64], 30% of patients with SLE (Middleton, 1994), but its comparable with the prevalence of diabetes mellitus 17% (Tishler, 2000), it's higher when compared to a prevalence rate of FMS in chronic hemodialysis 7.4% (Tolga Enver, 2005), bronchial asthma 8.3% (AL-Rawi, 2003); and behcets disease 8.9% (Al-Izzi, 2001). In this study females with hypothyroidism outnumber male patients reflecting the sex ratio conventionally observed in general hypo-thyroidism population (Okosieme, 2011).

There were a high proportion of female with hypothyroidism having FMS compared to male patient (ratio 9:1) also CWP was encountered more in female patients which is in agreement with other study (Kevin, 2011). CWP dose not absolutely correlate with the presence of FMS as most patient with CWP have fewer than 11 of 18 tender points (Giles, 2000). The high of FMS found in our study may be explained by the age of our inclusion sample (16-60 years old) where FMS more frequent in age of ≥40 years. Indeed, studies consistently show that FMS is more common in middle age individuals (Carmona, 2001). The prevalence of FM in patients with chronic diseases appears to be significantly high (Bourikas, 2009). Most of our patients are with BMI between 18.5-24.9 kg/m and FMS was reported in female which showed increased BMI (Munshid, 2010). Hypothyroidism patients with disease duration more than five years were more prone to have FMS, high proportion of our patients with FMS were had hypothyroidism for more than 5 years with significant relationship (P=0.0008, where

**Table 1. Demographic distribution of hypothyroidism patients and control by age and gender**

| | Hypothyroidism patients N=124 | Mean ± SD | Controls N=124 | Mean ± SD |
|---|---|---|---|---|
| Age | | | | |
| 16-29 | 13(10.5%) | 42.5 ± 12.8 | 7 (5.6%) | 42.5 ± 12.8 |
| 30-39 | 36 (29%) | | 30 (24.2%) | |
| 40-49 | 47 (37.9%) | | 53 (42.8%) | |
| 50-59 | 17 (13.7) | | 19 (15.3%) | |
| > 60 | 11 (8.9) | | 15 (12%) | |
| Gender | | | | |
| Female | 74 (59.7%) | | 70 (56.5%) | |
| Male | 50 (40.3%) | | 54 (43.5%) | |

**Table 2. Distribution of hypothyroidism patients and control by body mass index (BMI)**

| BMI | Hypothyroidism patients N=124 | Control N=124 |
|---|---|---|
| Underweight 16-18 kg/m$^2$ | 0 0.0% | 0 0.0% |
| Normal 18-25 kg/m$^2$ | 75 60.5% | 70 56.5% |
| Overweight 25-30 kg/m$^2$ | 34 27.4% | 38 30.6% |
| Obese ≥ 30 | 15 12% | 16 12.9% |

**Table 3. distribution of study sample according to the presence of hypothyroidism and fibromyalgia syndrome (FMS)**

| | Hypothyroidism | Control | Odd's Ratio | P-value |
|---|---|---|---|---|
| FMS | 22 (17.7%) | 5 (4.0%) | 5.13 | 0.001 |
| No FMS | 102 (82.3%) | 119 (96.0%) | | |
| Total | 124 | 124 | | |

**Table 4. The prevalence of (FMS) among hypothyroidism patients by the age, gender, and BMI**

| | | FMS | | Total | P-value |
|---|---|---|---|---|---|
| | | positive N=22 | negative N=102 | | |
| gender | Female | 19 (25.7%) | 55 (74.3%) | 74 | 0.01 |
| | Male | 3 (6%) | 47 (94%) | 50 | |
| Age | < 40 | 7 (14.3%) | 42 (85.7%) | 49 | 0.566 |
| | >40 | 15 (20%) | 60 (80%) | 75 | |
| BMI | < 25 | 18 (22%) | 64 (78%) | 82 | 0.14 |
| | ≥ 25 | 4 (9.5%) | 38 (90.5%) | 42 | |

**Table 5. Comparison between hypothyroidism patients with and without (FMS) according to duration of disease, number of relapse periods & doses of levothyroxine**

| | | FMS | | Total | P-value |
|---|---|---|---|---|---|
| | | positive N=22 | negative N=102 | | |
| Duration of | < 5 years | 6 (7.9%) | 70 (92.1%) | 76 | 0.0008 |
| hypothyroidism in years | ≥ 5years | 16 (33.3%) | 32 (66.7%) | 48 | |
| No. of relapse periods/year | 1 | 8 (10.5%) | 68 (89.5%) | 76 | 0.016 |
| | ≥ 2 | 14 (29.2%) | 34 (70.8%) | 48 | |
| Levothyroxine | ≤ 50 µg | 12 (16.6%) | 60 (83.4%) | 72 | 0.896 |
| | >50 µg | 10 (19.2%) | 42 (80.8%) | 52 | |

**Table 6. Comparison between hypothyroidism patients and control variables by chronic wide spread pain (CWP)**

| | | Hypothyroidism N=124 | Control N=124 | P-value |
|---|---|---|---|---|
| **CWP** | YES | 42 (33.9%) | 35 (28.2%) | <0.0001 |
| | NO | 82 (66.1%) | 89 (71.8%) | |

diffuse pain that has been present for years is likely to be due to FMS (Clauw, 2008). In present study 29.9% of FMS among hypothyroidism patients had frequent relapse periods per year (P= 0.016) reflect the association with an increased risk of FMS ,which is in agreement with other study (AL-Rawi, 2003) . Depression and tiredness are common in hypothyroidism patients (Okosieme, 2011), which may predispose to FMS (Clauw, 1995). Both middle age and female gender are known risk factors for chronic pain determined by biological and social factors, non paid work (e.g. household work) is per se a risk factor for pain (Ana Assumpaco, 2009).

The diagnosis, assessment, & follow up of FMS relies on self reported syndrome, commonly pain and tenderness is subjective reflecting many factors like, ethnicity, age, sex, social back ground, underlying concomitant chronic disease and psychological stress (Hazleman, 1998). This is also true regarding management, there is no specific treatment for FMS (Gursel, 2001). A number of limitations of the current study must be pointed out. In the present study did not perform a detailed assessment of depression, anxiety, or coping among patients who developed tenderness and other symptoms of FMS.

More detailed analyses of these parameters would better characterize these aspects and would assist in the evaluation of the association between hypothyroidism and the development of FMS symptoms. The relatively small size of the study sample must be noted. Despite these limitations, our findings call attention to important relationship between FMS and hypothyroidism. The association of FMS and hypothyroidism may pose diagnostic dilemmas, where may contribute to a misinterpretation in initial diagnosis and relapse period, also this association lead to frequent physician visits, early retirement, loss of income, and social isolation (Palm, 2001). Treatment of FMS is by education, certain medications, cognitive behavioral therapy and exercise (Simms, 1988). FMS recognition in hypothyroidism is fundamental for adequate treatment of patient who hold both diseases at the same time.

**Conclusion**

Chronic wide spread pain (CWP) and fibromyalgia syndrome (FMS) are positively correlated with hypothyroidism an association not previously reported in our locality. FMS is more common in female who had disease duration ≥ 5 and within middle age. No role of Levothyroxin in the present study.

**Recommendation**

- FMS recognition in hypothyroidism is fundamental for adequate treatment of patient who hold both diseases at the same time.
- A –another study needed like cohort study to established relationship between FMS and hypothyroidism .
- In future need studies on risk factor of FMS .

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**Appendix 1:**

**Criteria for the classification of fibromyalgia+**

1. History of widespread pain / definition. Pain is considered widespread when all of the following are present: pain in the left side of the body, pain in the right side of the body, pain above the waist, and pain below the waist, an addition, axial skeletal pain (cervical spine or anterior chest or thoracic spine or low back) must be present. In this definition, shoulder and buttock pain is considered as pain for each involved side, low back pain is considered lower segment pain.
2. Pain in 11 of 18 tender points on digital palpation. * definition. Pain on digital palpation, must be present in at least 11 of the following 18 tender point sites:

- Occipit: bilateral, at the suboccipital muscle insertion.
- Low cervical: bilateral, at the anterior aspect of the intertransverse spaces at C5-C7.
- Trapezius: bilateral at the midpoint of the upper border.
- Supraspinatus : bilateral, at origins, above the scapula spine near the medial border.
- Second rib: bilateral, at the second costochondral junctions, just lateral to the junctions on upper surfaces.
- Lateral epicondyle: bilateral 2 cm distal to the epicondyles.
- Gluteal : bilateral, in upper outer quadrants of buttocks in anterior fold of muscle.
- Greater trochanter: bilateral, posterior of the trochantric prominence.
- Knee: bilateral, at the medial fat pad proximal to the joint.

+ For classification purposes, patients will be said to have fibromyalgia if both criteria are satisfied. Widespread pain must have been present at least 3 months. The presence of a second clinical disorder dose not exclude the diagnosis of fibromyalgia. *Digital palpation should be performed with an approximate force of 4kg. for a tender points to be considered positive the subject must state that the palpation was painful, "tender" is not to be considered "painful".

**Appendix 2**

**Questionnaire Form**

**Fibromyalgia in patient with hypothyroidism**

- ❖ Patient's number: date: / /

**Name:** Consent:
**Age:**
**Sex:** Wt:
**Occupation Ht:**

- ❖ Fibromyalgia features :
- Duration of wide spread pain :
- Tender point :
- ❖ Associated features :

Sleep disturbance
Head ache: Anxiety:
Fatigue depression:
Numbness irritable bowel

- ❖ Drugs
- ❖ Investigations:

CBP ESR
LFT RFT
S.Ca S.K S.A.P

**Hypothyroidism**

Duration
Controlled uncontrolled
**Levothyroxin**
≥ 50µg < 50µg
**NO. OF Relapse** :

**List of abbreviations**

| | |
|---|---|
| ACR | American College Of Rheumatology |
| BMI | Body Mass Index |
| CNS | Central Nervous System |
| CSF | Central Spinal Fluid |
| CWP | Chronic Widespread Pain |
| e.g. | For example |
| FMS | Fibromyalgia Syndrome |
| Kg | Kilogram |
| mg | Milligram |
| No. | Number |
| SLE | Systemic Lupus Erythematosus |
| Wt. | Weight |
| TSH | Thyroid Stimulating Hormone |
| T4 | Thyroxine |
| T3 | Triidothyronine |
| ICD | International Classification of Diseases |
| CBT | Cognitive Behavioral Therapy |

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