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The Musculoskeletal Manifestation Among Patients with Different Thyroid Diseases and The Role of Thyroid Hormones on Musculoskeletal System

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ABSTRACT

Thyroid disease is a leading public health problem that has increased globally over the past decades. Thyroid diseases have been observed in more than 100 countries and affecting approximately 1.6 billion populations worldwide. Musculoskeletal disorders (MSDs) are very common in thyroid disease patients and TH stimulates both protein synthesis and degradation. An alteration in TH levels is often responsible for a specific myopathy and the deposition of mucopolysaccharides, notably hyaluronic acid in articular and periarticular structures Various knee musculoskeletal ultrasound findings, osteophytes, enthesophytes, synovitis, cortical erosion, enthesitis, joint effusion. Thyroid dysfunction patients with associated risk factors such as aging female gender and hyperuricemia are at a greater risk of musculoskeletal disorders.

Keywords: public health problem, Thyroid diseases, protein synthesis, aging female gender

Introduction

The thyroid gland is one of the most important endocrine glands of the body. The gland secretes the thyroid hormones, which maintain the level of metabolism in the tissues that is optimal for their normal function. Thyroid hormones stimulate O_2 consumption by most of cells in the body, help to regulate lipid and carbohydrate metabolism (Alahmar *et al.,* 2019**)**. Thyroid hormones are essential for growth, neuronal development, reproduction and regulation of energy metabolism (Shah *et al.,* 2021). In fact, this little butterfly-shaped part of the endocrine system is essential to everyday health. Thyroid function is controlled by the thyroid-stimulating hormone (TSH) which secretd by the anterior pituitary. The secretion of this hormone is in turn increased by thyrotropin-releasing hormone (TRH) from the hypothalamus and which is subjected to negative feedback control by high circulating levels of thyroid hormones acting on the anterior pituitary and the hypothalamus (Johnstone *et al.,* 2014).

Symptoms of musculoskeletal affection are frequently seen in thyroid disorders because the endocrine system has a complex influence on the structure and function of musculoskeletal tissues. The relationship between diseases of the thyroid gland and rheumatic pathology is significant and multifactorial. Endocrine disorders can involve a variety of tissues, including bones, muscles, nerves, and joints. That is why, endocrine arthropathies, myopathies, and other musculoskeletal disorders should all be considered in the differential diagnosis of musculoskeletal injury (Voloshyn *et al.,* 2022)

Rheumatic manifestation with thyroid dysfunction

In hyperthyroidism

- Painless proximal myopathy (70 %).
- Shoulder periarthritis (adhesive shoulder capsulitis) (7 %).
- Thyroid acropachy.
- Osteoporosis, osteopenia (Moutsopoulos *et al.,* 2021).

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In hypothyroidism

- Carpal tunnel syndrome (15 % of hypothyroid Patients).
- Raynaud 's phenomenon.
- Hypothyroid myopathy (affects almost 80 % of
- Patients with hypothyroidism).
- Arthropathy (25 % of patients with hypothyroidism).
- Hoffman's syndrome.
- In patients with autoimmune thyroiditis, rheumatic

Manifestations (osteoarthritis, fibromyalgia, raynaud's Phenomenon, sicca symptoms, and arthritis) frequently Occur even in the absence of overt thyroid Dysfunction (West, 2020).

Euthyroid patients with chronic lymphocytic thyroiditis

- Arthralgias were a presenting complaint in 98 % of patients.
- Fibromyalgia syndrome was found in 59 % of patients.
- Raynaud's phenomenon occurred in 28 % And sicca symptoms in 26 % of patient. (West, 2020).

Pathophysiology of muscle and bone affection

Skeletal muscle is among the principal thyroid hormone's (TH) target tissue, where TH regulates proliferation, metabolism, differentiation, homeostasis and growth. In physiological conditions, TH stimulates both protein synthesis and degradation (Mullur *et al.,* 2014).

The alteration in TH levels is often responsible for a specific myopathy. Intracellular TH concentrations are modulated in skeletal muscle by a family of enzymes named deiodinases; in particular, in muscle, deiodinases type 2 (D2) and type 3 (D3) are both present. D2 activates the prohormone T4 into the active form triiodothyronine (T3), whereas D3 inactivates both T4 and T3 by the removal of an inner ring iodine. Regulation of the expression and activity of deiodinases constitutes a cell-autonomous, pre-receptor mechanism for controlling the intracellular concentration of T3. Skeletal muscle relaxation and contraction rates depend on T3 regulation of myosin expression and energy supplied by substrate oxidation in the mitochondria. The balance between D2 and D3 expression determines TH intracellular levels and thus influences the proliferation and differentiation of satellite cells, indicating an important role of TH in muscle repair and myogenesis. During critical illness, changes in TH levels, thyroid hormone receptor and deiodinase expression negatively affect skeletal muscle function and repair (De Stefano *et al.,* 2021).

Variety of musculoskeletal manifestations in thyroid diseases ranging from early growth defects during infancy to adult manifestations includes myalgias, arthralgias, myopathy, bone disorders, acropachy and arthritis (Voloshyn *et al.,* 2022).

Rheumatological manifestations in patients with hypothyroidism result from hormonal dysfunction and deposition of mucopolysaccharides, notably hyaluronic acid in articular and peri-articular structures.

Indeed, the excess of hyaluronic acid in patients with primary hypothyroidism is due to the stimulation of hyaluronic acid synthesis by the increased TSH levels and the inhibition of hyaluronic acid degradation caused by thyroxine deficiency (Clunie *et al.,* 2018).

The role of TSH in the pathogenesis of arthropathy was also highlighted because normalization of TSH levels under thyroid hormone substitution therapy leads to improvement and complete resolution of articular symptoms. However, other studies showed that rheumatic manifestations may occur in patients with chronic lymphocytic thyroiditis, even in those with TSH levels within normal ranges (Apuzzi *et al.,* 2021).

Locomotor manifestations of thyroid dysfunction

Joint manifestation: (Tagoe *et al.,* 2019)

The association with autoimmune thyroid diseases (AITD) and rheumatic syndromes may involve metabolic processes as well as immunologic and inflammatory pathways. AITD, particularly as CLT, has been associated with several musculoskeletal (MSK) syndromes including osteoarthritis (OA) and inflammatory arthritis.

The prevalence of well-defined connective tissue disease (CTD) is also increased with AITD, which shares genetics with CTD.8–10 The arthritis, although generally non-erosive, can be aggressively degenerative and sometimes associated with erosive OA (Tomer 2014).

Recently, chronic widespread pain and fibromyalgia syndrome (FMS) have also been linked to AITD, in particular CLT, with a prevalence rate approaching 30–40%. Most reports of the association of AITD with MSK conditions have been from small studies and were assumed to be hormonally derived (Tagoe *et al.,* 2012).

However, many subjects with MSK signs and symptoms have no evidence of hormonal imbalance.

In thyroid disease the ability of TPOAb to fix complement has been suggested as contributing to the mechanism of injury of AITD.

Similar to the finding of TPOAb being more closely associated with thyroid destruction and hypothyroidism than TgAb, some studies have suggested a closer association of TPOAb with some MSK manifestations including FMS in rheumatoid arthritis (Bazzichi *et al.,* 2007)

In a recent study, total thyroidectomy with subsequent reductions in the levels of TPOAb improved symptoms in subjects with TPOAb levels in excess of 1000IU/mL, suggesting immunological pathophysiological mechanisms over hormonal mechanisms of injury in AITD-related disease.

Most cases of arthropathic changes in adult-recognized hypothyroidism involved the knees and hands, polymyalgia rheumatica, nerve entrapment and tenosynovitis Adhesive capsulitis, also known as frozen shoulder (Tagoe *et al.,* 2019).

Some study had suggested that treatment with levothyroxine may cause long-term osteoporosis, hyperthyroidism is one of the endocrine diseases classically associated with osteoporosis. The effect of hyperthyroidism on bone remodeling and metabolism has been thoroughly described, as T_4 and T_3 can directly stimulate bone resorption *in vitro.* In addition, the normal bone remodeling cycle is reduced from 200 to 113 days, mainly at the expense of the formation period with a failure to replenish the bone. Both the formation markers of bone resorption may be elevated (Tárraga López *et al.,* 2011).

Patients with endogenous hyperthyroidism have reduced BMD compared with euthyroid controls. It has been shown that the treatment produced a significant increase in trabecular BMD.

Exogenous administration of suppressive doses of thyroxin may have a negative effect on BMD. One study found a decrease in femoral neck BMD in pre-and post-menopausal women with thyroid carcinoma treated with suppressive doses of thyroxin; the reduction in lumbar spine BMD was significant only in post-menopausal women. Other controlled studies show no changes in BMD with suppressive therapy (Delitala *et al.,* 2020).

Muscular manifestation

Both hyperthyroidism and hypothyroidism are associated with myopathy, Hoffman's syndrome, rhabdomyolysis, acute compartment syndrome (Ataallah *et al.,* 2021)

Hoffmann's syndrome is an unfrequent form of myopathy dependent on severe hypothyroidism, characterized by proximal myopathy, hypertrophy of muscles and often painful muscle cramps. The pseudohypertrophy of the muscles seems to be linked to the accumulation of glycosaminoglycans in the muscles of the extremities, more marked on the limbs with the gastrocnemius muscle, conferring to the patient an athletic appearance (Finsterer *et al.,* 2016).

Muscle enzymes are elevated and hormonal correction of hypothyroidism causes a gradual improvement in myopathy with normalization of muscle enzymes.

Acute compartment syndrome is an uncommon complication of uncontrolled hypothyroidism. If unrecognized, this can lead to ischemia, necrosis and potential limb loss.

In recent years, cases of myalgia during the treatment of hyperthyroidism have been presented, and the side effects of anti-thyroid drugs and relative hypothyroidism have been proposed as explanations for these muscle symptoms. Carbimazole is a commonly used antithyroid drug (ATD), which is associated with several well-established side effects. However, carbimazole-induced rhabdomyolysis is rare (Lu *et al.,* 2020).

1. Neural manifestation

Neuropsychiatric, Neuromuscular dysfunctions were shown to be common in thyroid diseases, ranging from 20% to 80%

Hypothyroidism is associated with psychiactric manifestation like depression and mania, while hyperthyroidism is linked with dementia and mania. The association between Graves' disease and various mental disorders such as depressive and anxiety disorders .

Also hypothyroidism usually affects both the central and peripheral nervous systems. Patients have reflex loss, proximal muscular weakness, numbness, paresthesia, reduced sensations, and slower muscle contraction and relaxation as a result of their peripheral neuropathy (Hussein *et al.,* 2021)

Thyroid illness can manifest with neurological consequences initially, or it can develop alongside other neurological diseases, especially those with an autoimmune origin. As a result, neurologists frequently meet thyroid illness patients. Polyneuropathy has been linked to hypothyroidism in numerous previous studies (Simon *et al.,* 2009)

Peripheral polyneuropathy is caused by a deficiency in the nerve cell body, axons or myelin sheath, and it causes reduced nerve conduction velocities and amplitudes. The sural and median nerves are the most usually impacted nerves, as the distal and sensory nerves are affected first. Carpal tunnel syndrome, caused by entrapment of the median nerve, is the most common cause of peripheral nerve injury in hypothyroidism (Churilov *et al.,* 2019)

Graves' disease (GD) is the most prevalent cause of spontaneous hyperthyroidism and is a common cause of ocular myasthenia.

GD might be difficult to diagnose since the visual symptoms of both disorders are quite similar. From a therapeutic and prognosis standpoint, the diagnosis is critical. Myasthenia is aggravated by undiagnosed and untreated hyperthyroidism, which can occasionally lead to a fatal myasthenic crisis.

Sensory neural hearing loss and ophthalmopathy are two symptoms of cranial nerve involvement in thyroid disease. Patients with hypothyroidism were found to have hearing loss in about 37% of cases. (Hussein *et al.,* 2021)

Bone and Joint Conditions Possibly Associated with Hypothyroidism

1. Epiphyseal dysgenesis
2. Slipped capital femoral epiphysis
3. Aseptic necrosis
4. Pseudogout/gout
5. Erosive osteoarthritis

Association with hyperthyroidism

1. Osteoporosis.
2. Osteopenia.
3. Bone fracture.
4. Arthragia.

Diagnosis of musculoskeletal affection

Imaging tests

X-rays

X-rays are quick and simple way of detecting bony problems, such as a suspected fracture. They are used to also to rule out problems such as arthritis, infection, tumours, or deformity. X-rays do not show soft tissue problems such as tendon, ligament or muscle injury (Huffer, 1988)

CT (computed tomography) Scan

CT scans are best at looking at bone and give much more detail than ordinary X-rays. They are useful for finding fractures or bony problems that are not visible on normal X-raysMRI (magnetic resonance imaging) Scan (Isida *et al.,* 2015).

MRI scans are excellent at looking at soft tissues such as muscles, ligaments, tendons and cartilage. At International Orthopaedic Clinic we understand that some patients feel claustrophobic in

a normal MRI scanner. We have access to open scanners which will make you feel more comfortable. (Shahzad *et al.,* 2020).

- **Ultrasonography**

Ultrasound is a fast and simple way to identify inflammation around joints and tendon tears. It is also useful to guide a needle into a joint (D'Agostino *et al.,* 2013).

Line of treatment of musculoskeletal affection

a) Exercise therapy is beneficial for pain, function, and quality of life, Current research evidence shows significant positive effects in exercise programs on pain, function, quality of life, and work related results in the short and long term for all manifestations of musculoskeletal pain (compared to subjects without exercise) (Rush *et al.,* 1994).
b) Ultrasound and shock wave therapy do not significantly improve the clinical outcomes of acute and chronic lower back pain (Kertzman *et al.,* 2015)
c) Psychosocial interventions in combination with other treatment options provide an additional benefit for all manifestations of musculoskeletal pain, especially for patients found to have a poor prognosis before treatment. The outcome of psychosocial treatment is also influenced by other factors such as the patient's prognosis, the healthcare provider providing the treatment, the treatment delivery settings and the treatment components (Luskin *et al.,* 2000)
d) NSAIDs and opioid analgesics (especially for acute pain) were generally effective, but the beneficial effects were evident mostly in the short term Selective cyclooxygenase (Cox) -2 inhibitors (e.g., celecoxib) were found to be effective in relieving musculoskeletal pain. However, they are associated with higher risks of adverse cardiovascular and gastrointestinal reactions compared to nonselective NSAIDs. NSAIDs, Cox-2 selective inhibitors, and opioids reduce pain in the short term, but the magnitude of the effect is modest and the potential for adverse effects such as gastrointestinal bleeding and opioid-induced hyperalgesia needs to be careful (Kehlet *et al.,* 1999).
e) One of the treatments used for musculoskeletal disorders are pharmacological interventions-injections for local application of the drug. There is evidence of short-term (4 weeks) benefits of corticosteroid injection to relieve moderate to severe shoulder pain for corticosteroid injection compared to NSAIDs. Also, for knee pain, corticosteroid injections have been shown to be short term effective in relieving moderate to severe pain. Musculoskeletal Ultrasonography in thyroid diseases (Cohen *et al.,* 2009).

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