

**SUMMARY POINTS**

- Both hypothyroidism and thyrotoxicosis may prominently affect the musculoskeletal system.
- Hypothyroidism may mimic rheumatic diseases.
- Patients with connective tissue diseases may be at increased risk of autoimmune thyroid disease.

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## Musculoskeletal Manifestations of Thyroid Disease

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Thyroid dysfunction can result in musculoskeletal symptoms that can mimic known rheumatic syndromes. In addition, the risk of specific thyroid diseases is increased in some autoimmune diseases. Rarely, medications used to treat thyroid diseases may cause musculoskeletal syndromes, and medications used to treat rheumatic diseases may affect the assessment of thyroid function. For these reasons, thyroid abnormalities must be considered when evaluating and treating a patient with musculoskeletal complaints or treating known rheumatic disease.

## Musculoskeletal Manifestations of Hypothyroidism

Thyroid hormones are essential to the growth, development, and continued optimal function of most tissues and organs. It is not surprising that the musculoskeletal system is affected by insufficiency of thyroid hormone (1).

### Effects in Children

The manifestations of congenital hypothyroidism (cretinism) and hypothyroidism occurring in childhood are usually dominated by cognitive deficiencies and developmental delays, but there are also specific associated abnormalities of the musculoskeletal system (2). Unless hypothyroidism is recognized and corrected, such children will be short with coarse features, widely set eyes, and a broad, flat nose. Linear growth is impaired with the limbs dis-

proportionately short in relation to the trunk. The most characteristic skeletal abnormality of early-onset hypothyroidism is epiphyseal dysplasia. This process may affect any bone in which epiphyseal closure has not yet occurred at the time of onset of hypothyroidism. It is best seen in large centers of endochondral ossification such as the femoral or humeral heads. Ossification occurs late, and, when it starts, there are several small centers of ossification in a misshapen epiphysis. The centers coalesce to form a single center with an irregular stippled appearance (2). An X-ray finding of stippled epiphyses is virtually pathognomonic of early onset hypothyroidism.

### Effects in Adults

Hypothyroidism more commonly occurs in adulthood. It may result from a variety of mechanisms including autoimmune (Hashimoto's), post-ablative ( $I_{131}$  or surgical), pituitary failure, or, in rare cases, iodine deficiency. In general, hypothyroid adults have manifestations consistent with a low basal metabolic rate. These include fatigue, weight gain, hair loss, constipation, cold intolerance, periorbital puffiness, and pale, cool, doughy skin. The relaxation phase of deep tendon reflexes is delayed. If untreated, the patient may enter a hypothermic stuporous state designated as myxedema coma, which may be fatal. An arthropathy involving stiffness of multiple joints with thick, non-inflammatory, highly viscous joint effusions may occur (3). The symptoms may be worse in the morning or after immobilization and, thus, may mimic rheumatoid arthritis. Occasionally, these patients may have an elevated erythrocyte sedimentation rate (1). Rarely, the arthropathy can be monoarticular (4). Also rarely, a destructive arthropathy involving the fingers, particularly the proximal interphalangeal (PIP) joints, may occur, which may resemble erosive

osteoarthritis (5,6). The arthropathy reverses with thyroid hormone replacement.

There have been conflicting reports on whether hypothyroidism is independently associated with chondrocalcinosis and pseudogout (3,7-9). If present, the association is probably weaker than that with other metabolic abnormalities such as hyperparathyroidism or hemochromatosis.

Hypothyroidism can be confused with fibromyalgia, a common condition (10,11). Hypothyroidism is relatively common in middle-aged women and may cause musculoskeletal aching and stiffness, as well as fatigue and lethargy. These manifestations are similar to those in fibromyalgia. Rarely, some hypothyroid patients may share similar disrupted sleep patterns with those with fibromyalgia (12). Nevertheless, hypothyroid patients do not commonly complain of sleep disturbance, nor do they usually have the wide variety of somatic complaints (irritable bowel, headaches, palpitations) so common in fibromyalgia. Also, fibromyalgia patients do not have the dry, thickened skin, hair loss, weight gain, and delayed reflexes common in hypothyroidism.

Hypothyroid patients often have an elevation of serum creatine phosphokinase (CPK) levels, which, with subjective weakness and muscle pain, may suggest the diagnosis of polymyositis (13). In fact, thyroid stimulating hormone (TSH) levels should be considered as part of the work up of a possible inflammatory myopathy. There are no true inflammatory infiltrates in the muscles in hypothyroidism and electromyography (EMG) is normal. Very rarely, hypothyroid patients may present with markedly elevated CPK levels and markedly increased muscle mass, an entity known as Hoffman's syndrome (14).

Hypothyroidism is associated with carpal tunnel syndrome, and thyroid abnormalities are generally sought in patients with this syndrome. One review noted a 10% incidence of hypothyroidism in patients with carpal tunnel syndrome (15).

Avascular necrosis of the hip has been reported at an increased frequency in hypothyroidism, and elevated cholesterol levels have been implicated (16).

**TABLE 1**

**Musculoskeletal Manifestations of Hypothyroidism**

- Noninflammatory arthropathy
- Fatigue and stiffness
- Chondrocalcinosis (possible)
- Carpal tunnel syndrome

An association of both hypothyroidism (17) and hyperthyroidism (18) has been alleged in polymyalgia rheumatica and giant cell arteritis, but not confirmed in recent years.

Patients with well-defined rheumatic diseases, such as rheumatoid arthritis or systemic lupus erythematosus, may have an increased association with hypothyroidism on an autoimmune basis (19,20). Patients with connective tissue diseases presenting with increasing fatigue in the absence of obvious increased inflammation should have their thyroid function checked.

**Musculoskeletal Manifestations of Thyrotoxicosis**

Thyrotoxicosis is the disease that results from the presence of excess thyroid hormone. This may result from an overactive thyroid gland (hyperthyroidism), ectopic production of thyroid hormone, or ingestion of excess exogenous thyroid preparations. Common manifestations include weight loss, tachycardia, anxiety, heat intolerance, and palpitations.

**Myopathy**

Thyrotoxicosis may lead to diffuse muscle weakness. This manifestation is more common in the elderly population, in which it may be unaccompanied by signs and symptoms of sympathetic hyperactivity (apathetic hyperthyroidism). This obviously makes diagnosis more challenging.

**Osteoporosis**

The most common musculoskeletal manifestation of thyrotoxicosis is decreased bone density (21,22). Thyrotoxicosis increases both osteoclastic and osteoblastic activity, but, on average, bone resorption predominates, particularly in trabecular bone (as opposed to cortical bone). Mech-

anisms likely to cause osteoporosis are decreased calcium absorption (related to decreased 1,25(OH)<sub>2</sub>VitD) and increased renal calcium excretion (21). Recently a study using DEXA (dual-energy X-ray absorptiometry) demonstrated a 7.4% reduction in lumbar spine bone density in hyperthyroid patients (23). It is unclear to what extent this decrease is reversible with appropriate treatment. In addition to laboratory evidence of osteopenia, there is epidemiologic evidence of an association of thyrotoxicosis with increased risk of fracture, at least in elderly white women (24).

More controversial is the relationship of the therapeutic use of suppressive doses of thyroxine, as often used in thyroid cancer or nodules, or excessive replacement doses and bone density. Several studies have demonstrated decreased bone density in women receiving suppressive thyroid therapy though others could not demonstrate this effect (25,26).

**Shoulder Pain**

Several authors have found an association between hyperthyroidism and periarthritis of the shoulder. In the 1950s, it was said that the shoulder pain may be resistant to therapy until the thyroid disease is controlled (27,28).

**Syndromes Associated with Graves' Disease**

Graves' disease is an autoimmune disorder caused by antibodies directed against the TSH receptor in the thyroid and is the most common cause of thyrotoxicosis in the United States. Some manifestations of Graves' disease are common to all hyperthyroid states (tachycardia, weight loss), whereas others are specific to this entity (ophthalmopathy). Graves' disease

**TABLE 2**

**Musculoskeletal and Dermal Manifestations of Thyrotoxicosis**

- Myopathy
- Osteoporosis
- Shoulder pain
- Pretibial myxedema
- Thyroid acropachy

is specifically associated with two other syndromes: pretibial myxedema and thyroid acropachy.

### Pretibial Myxedema

Pretibial myxedema (thyroid dermopathy) involves local thickening of the skin that occurs almost exclusively in patients with Graves' ophthalmopathy (29,30). It occurs in up to 4.3% of patients with Graves' disease and 15% of those with ophthalmopathy, usually after the eye disease is evident. The lesions usually begin as raised waxy areas in the pretibial region. They are usually light-colored but may be flesh-colored or yellow-brown. Hyperpigmentation and hyperkeratosis may be present, as well as induration and prominence of hair follicles. The most prominent histological change is thickening and replacement of the deep derms by mucinous material (31).

There are three broad classes of this disorder: 1) non-pitting edema with hyper-

keratosis, pigmentation, and skin discoloration; 2) separate or confluent plaques; and 3) a nodular form. While involvement of the pretibial region is most common, it also can occur in sites of old trauma as well as the face, neck, hand, abdomen, and elsewhere. The lesions are usually minimally symptomatic and therapy is conservative, generally with topical glucocorticoids although more aggressive therapy, including plasmapheresis and cytotoxic therapy, has been employed.

### Thyroid Acropachy

Thyroid acropachy is a rare syndrome occurring in Graves' disease that is strongly associated with ophthalmopathy and dermopathy (32). It has been estimated to occur in 1% of patients with Graves'. It is characterized by diffuse, soft finger swelling with clubbing and periostitis of the phalanges most commonly. The differential diagnosis includes hypertrophic pulmonary

osteoarthropathy (HPO), although there are distinguishing features. Acropachy spares the joints, and pain and inflammation are rare. Radiographically, the periosteal proliferation in HPO is more linear and regular.

### Medication Effects

Propylthiouracil, which is used to treat hyperthyroidism, has been rarely associated with systemic vasculitis (33). Methimazole, another antithyroid drug, rarely has been associated with autoimmune manifestations, including a lupus-like syndrome as well as antiinsulin antibodies and resultant diabetes mellitus. In addition, long-term glucocorticoid therapy (as often used in rheumatic diseases) may lower serum TSH levels and thus lead to the diagnostic consideration of thyrotoxicosis (34).

Therapy with salicylates may be associated with depression of protein-bound iodine, and radioactive iodine uptake (35).

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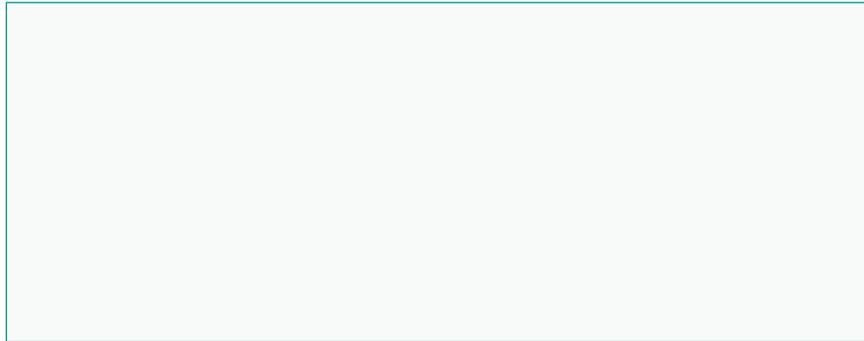
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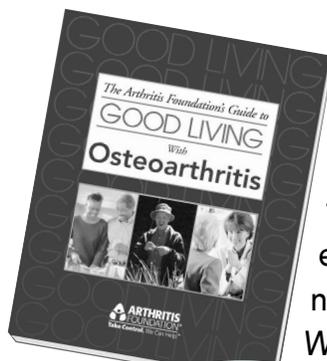
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