

# Endocrine myopathies: clinical and histopathological features of the major forms

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**Endocrinopathies, such as thyroid and parathyroid diseases, disorders of the adrenal axis, and acromegaly are included among the many causes of myopathy. Muscle disturbances caused by endocrine disorders are mainly due to alterations in the protein and carbohydrate metabolisms. Either a deficiency or excess of hormones produced by the glands can cause muscle dysfunction that can be reversed by starting hormone replacement therapy or acting on hormone dysfunction. The diagnosis is usually easy if a muscle disorder occurs in an overt endocrinopathy; however, in few patients, myopathy could be the first manifestation of the underlying endocrinopathy. In this article we discuss pathophysiology, clinical features and management of muscle involvement related to the major endocrine diseases.**

**Key words:** endocrine myopathies, muscle weakness, creatine kinase, hypothyroidism, myalgia, rhabdomyolysis

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## Conflict of interest

The Authors declare no conflict of interest

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## Introduction

Skeletal muscle disorders can arise from a variety of endocrine diseases, including those affecting thyroid, adrenal glands, pituitary, parathyroid. Either a deficiency or excess of hormones produced by the glands can cause muscle dysfunction that can be reversed by starting hormone replacement therapy or acting on hormone dysfunction<sup>1</sup>. The prevalence of neuromuscular diseases as a complication of endocrine disorders is not easily ascertainable and is likely to be underestimated. Non-specific muscular symptoms such as cramps, myalgias, proximal or generalized weakness and exertional pain, may be part of the variable clinical pictures of hypothyroidism, hyperparathyroidism, hyperadrenocorticism<sup>2</sup>. Moreover, in some cases as in hypothyroidism, myopathy becomes evident with increased CK levels, progressive proximal muscle weakness and electromyographic abnormalities<sup>1-3</sup>. Furthermore, some disorders can be considered typical of certain endocrinopathies, such as periodic paralysis in thyrotoxicosis. We review the main endocrine dysfunctions that can cause muscle disorders and their treatment.

## Thyroid disorders

Thyroid gland acts on several organ systems working as a metabolic regulatory centre through the secretion of L-thyroxine (T4) and

3,5,3'-triiodo-L-thyroxine (T3) whose production is regulated by thyroid stimulating hormone (TSH) <sup>4</sup>.

### *Hypothyroidism*

A thyroid hormone deficiency is often the result of a lack of dietary iodine, autoimmune thyroiditis or, less commonly, post-treatment ablation <sup>5</sup>. Hypothyroidism is usually more common in women. Symptoms are initially nonspecific and constitutional, with muscle cramps, ideomotor slowdown, later a myxedema may develop, with hair loss, thick skin, and heart enlargement. Hypothyroidism, when suspected, can be confirmed by measuring TSH and T4 blood tests <sup>6</sup>.

### **Hypothyroid Myopathy**

The percentage of patients affected by hypothyroidism experiencing neuromuscular symptoms varies from 30 to 80% <sup>4</sup>.

Proximal weakness, muscle stiffness and cramping, slow reflexes, and myoedema are the spectrum of neuromuscular symptoms of hypothyroidism and may exhibit also as presenting symptoms of the endocrine disease. Weakness is most common complaint followed by cramps <sup>3,4,7</sup>. Slow reflexes, best seen in the ankle jerk response, also represents a peculiar precocious sign of neuromuscular involvement in hypothyroidism <sup>8</sup>. Another possible acute presentation of hypothyroidism is rhabdomyolysis <sup>9,10</sup>.

Myoedema is uncommon and hence often undervalued by clinicians but it is, in most instances, one of classical signs of hypothyroid myopathy. It is a phenomenon of mounding of muscle tissue as a response to pressure or percussion <sup>11</sup>. Hypothyroidism may present as Hoffmann's Syndrome, which is a rare form of hypothyroid myopathy that occurs in adults and is characterized by the presence of hypothyroidism, pseudohypertrophy of muscles and varying degrees of muscle weakness <sup>3,12</sup>. Unusually, it is sometimes observed in children with hypothyroidism a muscular enlargement which is referred to as Kocher-Debre-Semelaigne syndrome <sup>13</sup>.

Muscular disturbances in hypothyroidism can be ascribed to the slow or reduced protein turnover and impaired carbohydrate metabolism due to the lack of thyroid hormone <sup>4</sup>.

### **Diagnosis and management**

It can be based on the following findings: a low thyroid hormone value, elevated up to ten times normal creatine kinase (CK) levels, possible myopathic pattern at the electromyography (EMG). Establishing a replacing therapy may lead to euthyroid state and muscle symptoms recovery <sup>4</sup>.

Morphological changes described in hypothyroid myopathy are largely non-specific and include fiber size variation, type 1 fiber predominance, type 2 atrophy, internal nuclei, sporadic necrosis and regeneration, glycogen accumulation, damaged mitochondria <sup>2,3</sup>. Core-like structures, mainly evident in type 1 fibers, are a frequent feature in long-standing overt hypothyroidism (Fig. 1A). These structures had histochemical and ultrastructural appearances of targetoid fibers and unstructured central cores, with evidence of abnormal deposition of intermediate filament proteins (i.e. desmin) at immunocytochemistry (Fig. 1B). At ultrastructural study, the core areas show disorganized myofibrils, Z-band streaming, rod formation, paucity of mitochondria and glycogen granules (Fig. 1C). Cores often disappear after treatment with levo-thyroxine.

### *Hyperthyroidism*

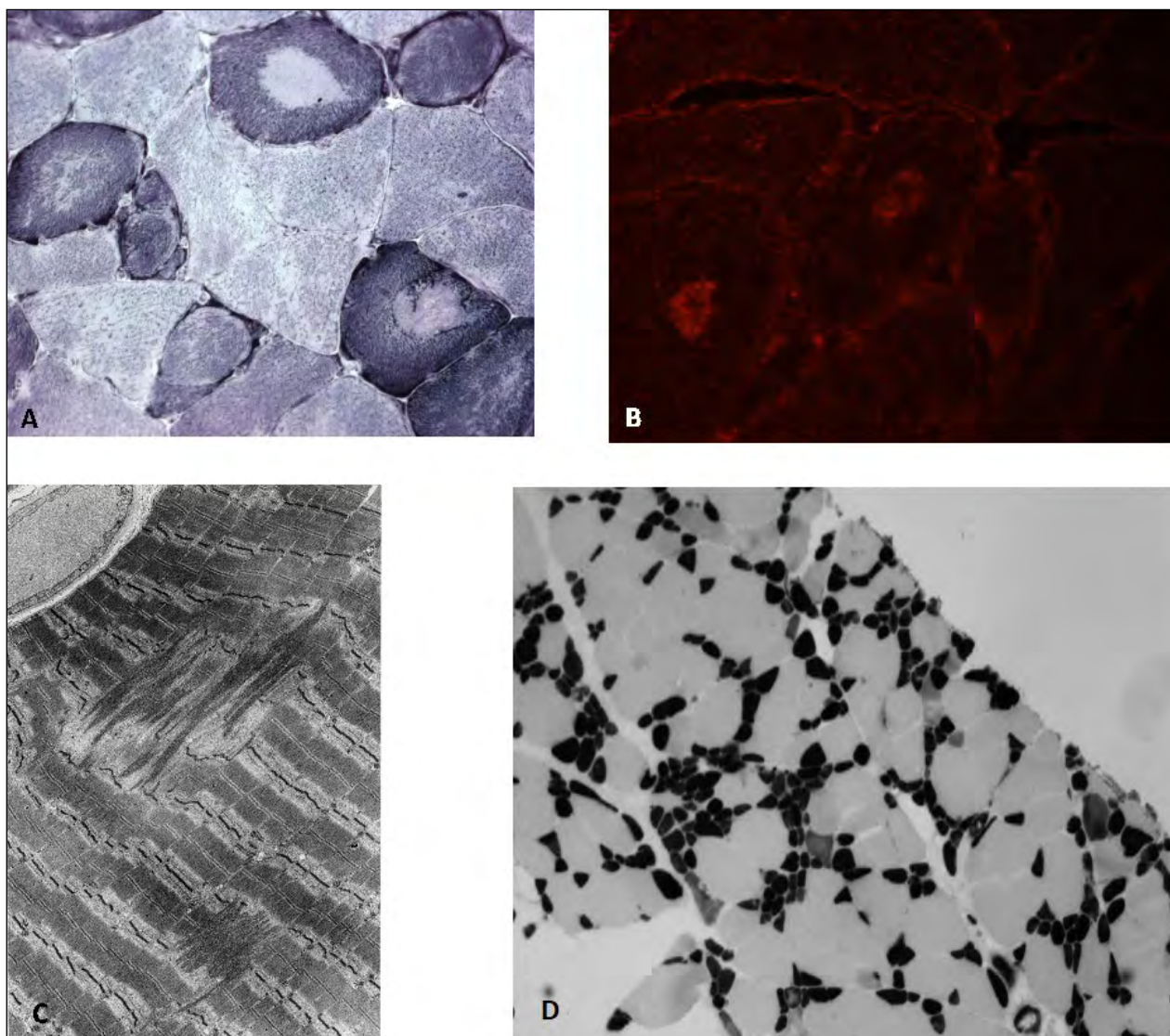
The prevalence of hyperthyroidism in women is between 0.5-2% and it is 10 times less common in men. The most common causes are Graves' disease, toxic multinodular goiter, and autonomously functioning thyroid adenoma. Rare causes of hyperthyroidisms are: pituitary adenoma, autoimmune thyroiditis (Hashitoxicosis), levothyroxine overdose, inadequate iodine supplementation (amiodaron induced hyperthyroidism, iodine-based contrast media), hCG excess (pregnancy, gestational trophoblastic disease, germ-cell tumors) <sup>14</sup>.

### **Hyperthyroid myopathy**

Muscle involvement has been reported to occur in about 80% of thyrotoxic patients <sup>15</sup>. Hyperthyroidism mainly leads to symptoms like muscle wasting and weakness such as proximal muscle weakness, involving both the upper and lower extremities, although distal muscle weakness is also described, associated to brisk reflexes. In addition to muscle weakness, muscle fatigue is often reported and generally described by patients as exercise intolerance.

Various authors have suggested that thyrotoxic myopathy is a result of the overall constellation of weight loss and generalized asthenia of hyperthyroidism <sup>15</sup>. In fact, thyrotoxic myopathy is rarely described as the onset symptom in thyrotoxic patients. However, cases of a fulminating myopathy in hyperthyroidism are reported, due to the involvement of respiratory and bulbar muscles <sup>16,17</sup>.

Thyrotoxic periodic paralysis are another rare manifestation of muscular disease in hyperthyroidism characterized by a rapidly progressing paralysis, greater in the proximal segments of lower limbs. This phenomenon occurs in susceptible individuals after an intracellular shift in potassium associated to a dilatation of sarcoplasmic reticulum; however, the underlying relation between dilatation of sarcoplasmic reticulum and excess of thyroid



**Figure 1.** Histopathological findings in hypothyroid and hypercortisolism associated myopathies A: cores in type 1 fibers, NADH-TR (magnification 280 X); B: immunocytochemistry revealing increased desmin binding in two cores (magnification 280 X); C: Electron microscopy showing two core areas with disorganized myofibrils, rod bodies, and lack of mitochondria and glycogen (magnification 6800X); D: ATPase pH 9.4 stain showing a marked type 2 fibers atrophy in steroid myopathy (magnification 110 X).

hormone is not clear. Thyrotoxic periodic paralysis manifests with hypokalemia in the acute state<sup>18</sup>.

The pathogenesis of muscle dysfunction in hyperthyroidism is likely due to an upregulation of metabolic activity which leads to increased catabolism in muscle cells, primary target of thyroid hormones.

#### Diagnosis and management

Muscle enzymes, including CK, are generally normal. At the EMG, a myopathic pattern can be observed. Muscle biopsy is frequently normal.

The management of these myopathies is based on achieving euthyroid state. It is demonstrated that beta-blocker agents, such as propranolol, improve muscle function<sup>4</sup>. On the other hand, it is important to obtain a smooth reduction of FT4 to minimize the risk of a hypothyroidism related myopathy, especially in patients susceptible to hormonal change<sup>19</sup>.

#### Parathyroid disorders

Parathyroid glands are four small glands of the endocrine system located behind the thyroid which have a

regulatory role with action as a thermostat in the systemic calcium homeostasis to ensure tight regulation of serum calcium concentrations and appropriate skeletal mineralization. They produce a hormone called parathyroid hormone (PTH) that raises the blood calcium level by increasing calcium gut absorption, bone resorption and reducing renal clearance of calcium ( $\text{Ca}^{++}$ )<sup>20</sup>.

#### *Hypoparathyroidism*

It results from PTH deficiency or end-organ unresponsiveness to PTH. Permanent hypoparathyroidism is the most common long-term complication after total thyroidectomy, but it can also occur as hereditary form, pseudohypoparathyroidism or as a consequence of severe hypomagnesemia. Its incidence varies from 30 to 60%<sup>20,21</sup>.

#### **Hypoparathyroidism myopathy**

Hypoparathyroidism rarely determines muscle involvement. However, mild CK elevation and muscle weakness have been described. More frequently, hypoparathyroidism results in hypocalcemia which leads to muscle tetany (increased neuromuscular irritability may be demonstrated by eliciting a Chvostek or Trousseau sign and poor reflexes)<sup>21</sup>.

#### **Diagnosis and management**

Calcium and magnesium serum concentration should be evaluated. CK in hypoparathyroidism can be normal or variably elevated<sup>22,23</sup>. No remarkable findings at EMG and muscle biopsy. A cardiological evaluation with QT interval analysis should be performed<sup>24</sup>. Correcting calcium and magnesium levels is the treatment guideline<sup>24</sup>.

#### *Hyperparathyroidism*

Hyperparathyroidism should result from primary hyperparathyroidism (HPT), which is due to a growth regulatory disturbance in one or several parathyroid glands (such as hyperplasia or adenomas), or from secondary hyperparathyroidism, which develops in patients with uremia, due to phosphate retention, hypocalcemia, and reduced active vitamin D levels, causing parathyroid hyperplasia and eventually development of parathyroid tumors and hypercalcemia<sup>25</sup>.

#### **Hyperparathyroid myopathy**

Hyperparathyroidism can develop both central and peripheral neurological symptoms. Muscle typical involvement is a proximal weakness with easy fatigability, atrophy and hyperreflexia<sup>26</sup>. In some cases, a clinical picture mimicking motor neuron disease has been reported, characterized by muscular atrophy and weakness with hyperreflexia and spasticity<sup>27</sup>.

#### **Diagnosis and management**

Creatinine kinase levels and EMG in hyperparathyroidism are usually normal. Muscle biopsy shows fibers atrophy usually not associated with degeneration. Surgical approach is considered the way to treat primary hyperparathyroidism leading to a regression of the myopathic disorder. Hyperparathyroidism secondary to renal disease is more difficult to treat, but administration of vitamin D and reduction of phosphorous intake may be helpful<sup>28</sup>.

#### **Adrenal glands disorders**

Adrenal glands are responsible for glucocorticoids (GCs) production under the hypothalamus-pituitary-adrenal (HPA) axis. These glands are involved in several mechanism for homeostasis and metabolism. In particular, cortisol, whose production is stimulated by adrenocorticotropic hormone (ACTH), acts as suppressant of inflammation, in response to metabolic dysfunction and stress situations<sup>29</sup>.

#### *Hypercortisolism*

Hypercortisolism can arise from both an iatrogenic condition and an endogenous overproduction. Furthermore, several pathological states associated with muscle damage, such as sepsis, diabetes, acidosis, chronic obstructive pulmonary disease, cancer, are accompanied by an increase of GC production<sup>29</sup>.

#### **Iatrogenic hypercortisolism**

As a result of an overdosage of steroids, prescribed for therapeutic purposes, an iatrogenic steroid myopathy can occur. The onset is subacute characterized by proximal muscle weakness followed by atrophy<sup>30</sup>. Muscle atrophy results both by a decrease of protein synthesis and by an increase of protein degradation in skeletal muscles. It has also been suggested that GCs impair angiogenesis decreasing capillary number<sup>31</sup>.

#### **Diagnosis and management**

In corticosteroid myopathy CK value are usually normal. The EMG shows a myopathic pattern with small, polyphasic potentials and no spontaneous activity. A peculiar finding of steroid myopathy is represented by a selective and in some cases marked type 2 muscle fiber atrophy at muscle biopsy which could be useful in diagnosis, in particular to differentiate from an inflammatory myopathy (Fig. 1D)<sup>32</sup>.

Steroid myopathy treatment is based on safety steroid dose reduction to the lowest possible dose, using alternate-day dosing or switching to a nonfluorinated steroid<sup>32</sup>.



## Endogenous hypercortisolism

Endogenous hypercortisolism can be related to an overproduction of ACTH due to pituitary adenomas (Cushing's disease) or to an ectopic hormone secretion of either ACTH or GCs.

Patients affected by endogenous hypercortisolism may complain of muscle weakness, typically proximal. The clinical picture varies from myalgias to severe muscle weakness and atrophy. Patient examination in these cases reveal peculiar signs of steroid excess, such as moon facies, buffalo hump, abdominal striae.

## Diagnosis and management

Diagnostic findings in endogenous hypercortisolism are overall the same of those described for the iatrogenic one. Therapy is based on the removal of the oversecreting tissue, leading to a restoration of hormone homeostasis and to the resolution of the myopathy<sup>33,34</sup>.

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