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# Endocrine Myopathies: Clinical Review

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**Abstract**

Endocrinopathy is generally associated with hormonally-mediated systemic disorders. Myopathy is a result of this association and sometimes can be the first manifestation of endocrine diseases. This condition generally misdiagnosed as weakness and diagnosis and treatment of endocrine diseases are delayed. Especially cushing's disease, exogen glucocorticoid use, hypothyroidism, hyperaldesteronism and osteomalacia can mimic inflammatory myopathies clinically. Endocrine myopathies are group of disease which must be part of differential diagnosis who has proximal muscle weakness. Statin and glucocorticoid use come to the knowledge of physician because these are the most common cause of drug related proximal myopathy. While evaluating patient with proximal myopathy, thyroid function tests, vitamin D levels, parathyroid hormone must be measured and primary hyperaldesteronism work up when clinically suspicion occurs. Treatment of endocrine myopathies are based on correction of endocrine disorder.

**Keywords:** Proximal myopathy; Vitamin D; Statin; Cushing's disease; Parathyroid hormone; Primary hyperaldesteronism

## Introduction

Myopathy literally means muscle disease. Pattern of weakness in myopathy most commonly involve proximal upper and/or lower limb muscles symmetrically. Myopathy can also, less commonly, involve distal limb, neck, facial, ocular, pharyngeal, respiratory and cardiac muscles. There is a broad range of underlying causes including drugs, alcohol, endocrine disease, Idiopathic Inflammatory Myopathies [IIM], hereditary myopathies, malignancy, infections and sarcoidosis [1] (Table 1). Patient's medical and family history, severity of symptoms, beginning time of symptoms, other endocrine indicators such as weight loss, tachicardia, hair loss, muscle tenderness, stria and cushingoid features must be examined. Patients with non-neurological conditions, such as anaemia, depression or chronic infective and inflammatory illnesses can use the term 'weakness' to describe their fatigue [2]. The following features should help to differentiate fatigue from weakness. Patients with fatigue would describe generalised and non-specific difficulty in performing different tasks that becomes more pronounced as they continue to perform the activity [2]. Some simple bedside tests, such as difficulty of the patient in rising from a low chair with arms folded across the chest or combing her hair could be seperate weakness from fatigue. Also proximal myopathy get involved in neurological diseases such as as Guillain–Barre syndrome, Myasthenia gravis, Motor neuropathies and Motor neuron diseases [3]. Neurological disorders' clinical presentations are not only muscle weakness and fatigability but also double vision, drooping of eyelids and muscle fasciculations [3]. In the presence of these features would suggest alternative diagnosis. Some of genetic disorders can be with myopathy and endocrinopathy such as Hoffman syndrome and Kocher-Debre-Semelaigne syndrome. On the other hand Myotonic dystrophies, Curschmann-Steinert disease and proximal myotonic myopathy [PROMM], are associated with primary hypogonadism and insulin hypersecretion [4]. While evaluating patient with proximal muscle weakness endocrine diseases such as cushing's disease, thyroid disfuction, parathyroid disfunction, primary hyperaldesteronism and osteomalacia must be excluded. Patients with hypothyroidism have muscle symptoms frequently and proximal muscle weakness occurs in about one-third of them. On the other hand, myopathy related with hyperthyroidism occur 62% of patients. Altough myopathy due to hypocalcemia is rare, it's association with hypercalcemia is common and due to a retrospective study with fifty one symptomatic hyperparathyroid patient proximal myopathy was the commonest presentation [24/51]. A prospective study of Sharma et al., 37 patients who were diagnosed with endocrine myopathies, thyroid dysfunction was the most common cause [17 cases], followed by vitamin D deficiency in nine, adrenal dysfunction in six, parathyroid dysfunction in three, and pituitary dysfunction in two [5]. While myopathy due to hypothyroidism, hypoparathyroidism, hyperaldesteronism and statin use can cause serum creatin kinase elevation, hyperthyroidism, hyperparathyroidism and glucocoticoids can not. Statin use, hypo-hyperthyroidism, hyperparathyroidism and hyperaldesteronism can also present polymyositis like syndrome. Treatment of myopathy associated with endocrine diseases are based on correction of endocrine disorder (Table 2). In this condition there is no need additional investigation such as muscle biopsy, electrophysiologic studies or genetic tests.

## Statin Myopathy

The most common muscle-related adverse event resulting from statin use is myalgia. It's incidence reported in randomized controlled

| | |
|---|---|
| Endocrine myopathies | Hypothyroidism, Hyperthyroidism<br>Hyperparathyroidism, Hypoparathyroidism, Pituitary Dysfunction, Osteomalacia, Primary Hyperaldosteronism |
| inflammatory myopathies | polymyositis, dermatomyositis and inclusion body myositis, Vasculitis, lupus, scleroderma, rheumatoid arthritis, Sjögren's syndrome |
| Hereditary or congenital myopathies | limb girdle,facioscapulohumeral and Becker muscular dystrophy, proximal myotonic myopathy, glycogen and lipid storage disorders |
| Infections | HIV infection, influenza, hepatitis B and C,<br>enteroviruses, trichinosis, cysticercosis, lyme myositis, epstein barr virus |
| Toxic myopathies | statins, fibrates, corticosteroids, colchicine, antimalarial drugs, zidovudine, alcohol |
| Electrolyte disorders | Hypokalemia, Hypophosphatemia, Hypocalcemia, Hypernatremia or hyponatremia |

**Table 1**: Causes of proximal myopathy.

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| | Serum CK Elevation | Polymositis like syndrome | Treatment |
|---|---|---|---|
| Statin Myopathy | + | Yes | Stop treatment. After normalization of serum CK use alternative statin with lower dose or use ezetimib |
| Glucocorticoids | - | No | If endogen reasons treatment of endocrine disease.<br><br>If exogenous reason if possible dose reduction |
| Hypothyroidism | ++ | Yes | Treatment of underlying disease |
| Hyperthyroidism | - | Yes | Treatment of underlying disease |
| Thyrotoxicosis | -<br><br>Except thyrotoxic crisis | Yes | Treatment of underlying disease and beta-adrenergic blockade with propranolol |
| Hyperparathyroidism | + | Yes | Treatment of underlying disease |
| Hypoparathyroidism | ++ | Yes | Treatment with calcium and calcitriol |
| Pituitary Dysfunction | ++ | No | Treatment of underlying disease |
| Osteomalacia | ++ | No | Treatment of underlying disease |
| Primary Hyperaldosteronism | ++ | Yes | Serum potassium normalization and treatment of underlying disease |

**Table 2:** Endocrine disorders associated with myopathy.

trials ranging from 1.5% to 3.0% [6]. According to one large population-based cohort study the incidence rate of myopathy in lipid-lowering drugs was 2.3 per 10,000 person-years [7]. Risk of myopathy depends on dose [high dose>low dose] and preparation used. In other classification lipophilic statins such as simvastatin, atorvastatin and lovastatin are more likely to produce muscular effects than hydrophilic statins such as pravastatin, rosuvastatin and fluvastatin [8]. Muscle toxicity is more common when statins are combine with other drugs which inhibit Cytochrome P450 3A4 Isoenzyme [CYP3A4] like fibrates, macrolide group antibiotics and amiodarone. On the other hand, simvastatin, atorvastatin and lovastatin are metabolized by the hepatic [CYP3A4] enzyme system but pravastatin, rosuvastatin and fluvastatin do not dependent on CYP3A4 [7]. Other risk factors include older age, liver or renal disease, hypothyroidism, alcoholism and heavy exercise [2]. A retrospective study performed by Smith et al. did not find routine monitoring of Creatin Kinase [CK] for patients on statin therapy helpful [9]. It is unclear but incidence of asymptomatic serum CK elevation approximately %5 and such elevations are not important if the patients are asymptomatic and their CK elevation is less than 10 times normal serum value. If Myalgia occurs with or without CK elevation, myalgia usually improves after discontinuation of the drug but If the muscle strength is normal and the myalgia is tolerable, you can switch statin theraphy another preperation [10]. A retrospective study of Hansen et al. reported that resolution of muscle symptoms after a mean duration of 2.3 months following discontinuation of statin [11]. Once symptoms resolve, patients could be rechallenged with lower dose of the same statin or an alternative one like pravastatin or fluvastatin. If muscle symptoms and elevation of CK persist despite stopping statin, muscle biopsy is recommended to exclude alternative diagnoses. However, cases of statin-induced polymyositis and dermatomyositis like syndromes have been reported and such patients require immunotherapy with steroids or IVIg [10]. Non-statin treatment is an option for those with recurrent muscle symptoms despite the lower doses or change the preperation. The National Institute for Health and Clinical Excellence [NICE] recommends ezetimibe for those who would otherwise be started on a statin, but are intolerant.

## Glucocorticoids

Glucocorticoid [GC] use as medical treatment is the most common reason of drug related myopathy and steroid myopathy [12]. On the other hand, Cushing's Disease [CD] is the most common cause of endogenous hypercortisolism. CD is most commonly due to production of ACTH from a pituitary adenoma with an incidence of 39 cases per million population and is more frequent in women than in men with a gender ratio of 15:1[13]. Altough acne, muscle weakness, truncal obesity and buffalo hump are common sign of CD, striae[>1 cm wide], facial plethora and proximal myopathy are the spesific clinical features of disease [14]. Dexamethazone and Triamsinolone are the most risky but oral, inhaler and topical steroid use can cause myopathy [15-17]. Endogen and exogen GC myopathy pathway are same. Muscles are effected directly by GC's anti-anabolic and catabolic effects on muscles [18]. GC's decrease the rate of protein synthesis and increase the rate of protein breakdown [19]. They inhibit the stimulatory action of insulin and aminoacids and interrupt IGF-1 signals which play a key role in the protein synthesis [20]. Also GC activate the major cellular proteolytic systems such as the ubiquitin proteasome system, the lyso-somal system and the calcium-dependent systems [19]. Steroid myopathy has a typical pattern of muscle weakness affecting the lower limbs more than the upper limbs and the proximal part of a limb more than the distal part. Typically myalgia and muscle tenderness don't occur [21]. Myopathy risk rises dose and tıme relatively. There is wide variability in the time course of symptom onset from a few weeks to many months after therapy. Despite this variability, there is a general dose relationship with systemic glucocorticoid therapy. Glucocorticoid myopathy is unusual in patients treated with less than 10 mg/day prednisolone or its equivalent [22]. The higher the dose of glucocorticoid, the greater is the likelihood of developing myopathy and the more rapid is the onset of weakness [22]. There is no definitive diagnostic test for glucocorticoid myopathy [23]. Muscle enzymes are generally normal, there is no electromyography finding but may show low amplitude motor unit potentials and muscle biopsy has no signs of necrosis or inflammation [24]. GC use as treatment of inflammatory diseases such as myopathies conflict with reason of muscle weakness. The onset of weakness or deterioration of clinical features one or more months after glucocorticoid therapy, the presence of other cushingoid features and normal or decreasing serum muscle enzyme levels all indicate glucocorticoid myopathy. Marco A Minetto et al. published a clnical study at 2011 is about diferential diagnosis steroid myopathy and inflamatory myopathies. In conclusion of study, muscle fiber conduction slowing and decreased levels of circulating muscle proteins such as CK and myoglobin can be sensitive markers of steroid myopathy [21]. Treatment of steroid myopathy is disease spesific. If the reason is

ACTH indipendent adrenal adenoma the patient should be treated by unilateral adrenalectomy [14]. In cases of bilateral hyperplasia, bilateral adrenalectomy may be an option but this choise will result in adrenal insufficiency and require lifetime hormone replacement therapy with glucocorticoids and mineralocorticoids. Unilateral adrenalectomy of the largest gland has been recently proposed as a possible therapeutic alternative for patients [25]. Transsphenoidal adenomectomy is the choise for the most patients wih cushing's disease [26]. Myopathy related Exogeneus GC use treatment is if disease allow reduce the GC dose. Symptoms will improve within three or four weaks after reduce GC dose.

## Thyroid Function Disorders

### A) Hypothyroidism

The most common cause of primary hypothyroidism in the United States is autoimmunity [Hashimoto thyroiditis] [27]. Altough myopathy is a rare musculoskeletal manifastation of hypothyroidism muscle symptoms may manifest in 25% to 79% of adult patients with hypothyroidism [28]. These symptoms include pain, cramps, stiffness, easy fatigability and weakness. There are two syndromes which are associated with hypothyroidism and myopathy.

Hoffman syndrome is a rare disease with hypothyroid myopathy and increased muscle mass[pseudohypertrophy] and Kocher-Debre-Semelaigne syndrome is associated with cretinism and muscular pseudohypertrophy [27,29]. Hypothyroidism may present with isolated muscle weakness so it is useful to check thyroid function in all patients with proximal myopathy, even if the absence of other symptoms of thyroid disease. Physical examination findings may include muscle hypertrophy, proximal muscle weakness and delayed relaxation phase of deep tendon reflexes [27,29]. Serum muscle enzyme levels are frequently elevated in patients with hypothyroid myopathy and rise of muscle enzym is typically mild [CK<1000 IU/L] but polymyositis-like illness or rhabdomyolysis with dramatic elevations in CK levels do exist in the literature [30,31]. There is a correlation between CK levels and thyrotropin-stimulating hormone [TSH] levels but not with a degree of weakness [27,29]. Diagnosis may be supported by Electromyography [EMG], which is often normal but helps in distinguishing hypothyroid myopathy from other myopathies. On muscle biopsy, there is characteristic atrophy of type II muscle fibers, with relative hypertrophy in type I muscle fibers. Other nonspecific finding is internalized nuclei [32]. In most cases of hypothyroid myopathy, symptoms resolve within approximately 6 months of therapy with supplemental thyroxine [27,28,30].

### B) Hyperthyroidism

Causes of hyperthyroidism are autoimmunity, infection, drug-induced or iatrogenic. The most common cause of hyperthyroidism is Graves disease worldwide [27]. Altered bone metabolism, pretibial myxedema and rarely myopathy are musculosceletal manifestations of hyperthyroidism. Hyperthyroid myopathy has a similar presentation as hypothyroid myopathy with proximal muscle weakness manifesting early in the disease course in up to 62% of patients in one study [33]. Neuromuscular symptoms and clinical weakness correlated with free thyroxine [T4] concentrations [28,34]. In contrast with hypothyroidism, serum CK levels are typically normal and myopathic findings on EMG were rare [28]. In the literature most of studies sustain myopathy associated hyperthyroidism, some of them come out with weakness is a functional muscle disorder rather than myopathy [28]. Symptoms of weakness resolve within the therapy for hyperthyroidism [28,34,35].

### C) Thyrotoxicosis

Younger patients generally have sympatho-adrenergic symptoms and thyrotoxic myopathy is a rare clinical finding such as rhadbomyolysis and hypokalemic periodic paralysis [36]. Chronic thyrotoxicosis may affect bulbar muscles and can be fatal [37,38]. Bulbar myopathy develops in 16.4 percent of patients with chronic thyrotoxic myopathy [37]. Other clinical fatal syndrome is Tyhrotoxic Periodic Paralysis [TPP] [39]. TPP is a form of secondary hypokalaemic periodic paralysis and generally affect in the age group of 20-40 years male [40]. Chronic thyrotoxic myopathy is more common. About two-thirds of patients with hyperthyroid myopathy report proximal weakness that usually begins several weeks to several months after the onset of hyperthyroidism which is common in men then women [41]. Serum CK is generally normal, except in thyrotoxic crisis, but elevated aldolase occurs in approximately 30 percent of patients. Beta-adrenergic blockade with propranolol can improve muscle power, sometimes dramatically, by reducing catecholamine mediated pathways [42]. Thyrotoxic myopathy usually resolves after treatment and became euthyroid [41,43].

## Pituitary Dysfunction

Pituitary dysfunction can result with various endocrine disorders such as hypo-hyperthyroidism, gonadal dysfunction, adrenal hypo-hyperfunction, growth retardation and acromegaly or gigantism. Musculoskeletal effects of thyroid and adrenal dysfuction were mentioned above. Patients with acromegaly usually have mild proximal weakness without muscle atrophy. Muscles often appear enlarged. The duration of acromegaly, rather than the serum growth hormone levels, correlates with the degree of myopathy [1]. Serum CK levels generally increased. The average mean action potential duration in the deltoid and rectus femoris muscles in the acromegalics was significantly shorter than in a group of control [44]. Multiple treatment options exist for patients with acromegaly including surgery, radiotherapy, somatostatin analogs, dopamine agonists, and growth hormone receptor antagonists [45].

## Parathyroid Disorders

### A) Hypoparathyroidism

Hypocalcemia is associated with many musculoskeletal problems such as skeletal hyperostosis, neuromyotonia, myopathy and rhabdomyolysis [46]. Hypocalcemic myopathy is characterized by proximal muscle weakness, hyporeflexia, high levels of serum CK and fatigue [47]. Mucsuloskeletal symptoms are corrolate with severity of hypocalcemia and how quickly the calcium level drops [48]. While tetany, muscle cramps, carpopedal spasm, seizures, and laryngospasm are associated with acute hypocalcemia, non-specific symptoms such as fatigue, irritability and anxiety are associated with chronic hypocalcemia. There is no certain explanation about mechanism of serum CK elevation but in some reports CK is inversly associated with calcium levels [49]. This situation is relevant with disruption the membrane integrity of myocytes, resulting in a leakage of cytoplasmic enzymes such as CK [47]. A recent study retrospectively analyzed the clinical data of nine patients with idiopathic hypoparathyroidism during the years 2006-2010 by Dai et al. and found that mild to moderate muscle cell degeneration were present in almost all patients. The degree of muscle change was related to the duration but not the degree of hypocalcemia [50]. When this is recognized, treatment with calcium and calcitriol relieves symptoms and CK levels return to normal [47,49,51].

**B) Hyperparathyroidism**

Hyperparathyroidism is the most common reason of hypercalcemia at outpatient [52]. Hyperparathyroidism can cause many musculoskeletal manifestations such as osteitis fibrosa cystica, subperiosteal or articular erosions, chondrocalcinosis, pseudogout, tendon ruptures, myopathy and proximal neuromyopathy [46]. In 2008 due to a retrospective study with fifty one symptomatic hyperparathyroid patient proximal myopathy was the commonest presentation[24/51] [53]. Myopathy resembling polymyositis has been reported in literature but mechanism could not strictly describe [54,55].

In secondary hyperparathyroidism some cases have myopathy because of ıschemia by renal failure and arterial calcifications [56]. Myopathy at least some primary hyperparathyroidism has a neurogenic basis and this procces result from combination of PTH related muscle breakdown and altered muscle energy metabolism [46]. CK levels are normal or slightly elevated. Electromyographic features may be neurogenic or myopathic. A study with six-teen patients who had primary hiperparathyroidism has shown that Electromyograms of these patients had short-duration, low-amplitude motor unit potentials and distal sensory latencies were normal on the other hands typical myopathic features were absent on muscle biopsy [57].There is no need to spesific treatment for myopaty, symptoms will resolve several weeks after parathyroidectomy [46,54,57].

## Primary Hyperaldosteronism

Primary Hyperaldosteronism [PH] or Conn's disease is a condition resulting in refractory hypertension, hypokalemic paralysis or potassium-losing nephropathy. Tumors and unilateral or bilateral zona glomerulosa hyperplasia can cause this condition [58,59]. Severe muscle weakness is classic manifestation of PH and is usually related to coexistent hypokalemia. Hypokalemic Myopathy [HM] may resemble polymyositis clinically and pathologically and hard to distinguish both disease either clinically or pathologically [60]. Also rhabdomyolysis reported in literature [61,62]. Findings in these patients include muscle pain and weakness, significantly increased creatine kinase, myopathic changes on electromyography and inflammatory cell infiltration, regeneration, necrosis and intracellular vacuoles on muscle biopsy [58]. On the other hand, intracellular vacuoles can be present in inclusion body myositis but at HM, correction of hypocalemia muscle biopsy return to normal [60]. Treatment of primary hyperaldosteronism related myopathy is that serum potassium normalization and treatment of underlying disease. Surgical excison of tumor is first choise but it is not possible, spironolactone, angiotensin-converting enzyme inhibitors and calcium channel blockers can be alternative treatment [59,61,63].

## Osteomalacia

Rickets and osteomalacia have been associated with muscle weakness and hypotonia [64]. Proximal myopathy can effect clinically 13% of patients with osteomalacia [65]. In addition to general weakness, more specific proximal muscle deficits are commonly described, including difficulty rising from a seated position, ascending a flight of stairs, or lifting objects. It is well known that intra -and-extra cellular calcium levels are important for muscle cell contractility [66]. In the reports of myopathy with vitamin D deficiency, many subjects had multiple biochemical abnormalities involving calcium, phosphate and parathyroid hormone levels that can be corrected with vitamin D repletion [65,67]. At this point it is hard to determine that what real reason of myopathy is. In the literature, hypophosphataemia and association of muscle weakness pathophysiology is well known [68]. Experimental studies have also shown skeletal muscles do not contain vitamin D Receptors[VDR][66,69], which is believed to mediate the all of the known action of vitamin D [70]. There is a conflict about VDR in the literature. In 2013 Girgis et al. reported a review which is about VDR in muscle. They analized thirteen study about this issue and stated the conflict [71]. In 2010 Laurie Schubert et al. repoted an experimental study which is about vitamin D effects on muscles. Vitamin D treatment significantly improved muscle strength and increased serum phosphorus. Replation of only phosphorus also increased muscle strenght. The improvement of muscle strength correlates well with serum phosphorus levels [64]. This study also support vitamin D has no direct effect on muscles. In most cases of vitamin D deficiency, symptoms and laboratory findings such as ALP elevation hipocalcemia and hypophosphatemia resolve within the therapy with supplemental vitamin D [65,68,72].

## Conclusıon

Endocrine diseases are generally associated with hormonally-mediated systemic alterations in metabolism. At any time during the course of many endocrinopathies muscle may become affected. The diagnosis of myopathy may be more difficult if it is the first presentation of the endocrinopathy. Altough thyroid disorders and cushing disease are well known, literature is limited about endocrine myopathies. While using glucocorticoids and statins as a medication patients must be questionared about muscle weakness in every visit. It is important to understand endocrine myopathy because most cases misdiagnosed and treated like inflammatory myopathy. Also in most cases who has myopathy associated with endocrinopathy , their weakness is improved and serum CK levels normalized by treatment of underlying disease.

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