Brief Communication

Glucocorticoid-induced myopathy: Pathophysiology, diagnosis, and treatment

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ABSTRACT

Glucocorticoid-induced myopathy is the most common type of drug-induced myopathy. Nearly 60% of patients with Cushing's syndrome have muscle weakness. Glucocorticoid-induced muscle atrophy affects mainly fast-twitch glycolytic muscle fibers (type IIb fibers). This brief review will discuss the pathophysiology behind glucocorticoid-induced myopathy, along with diagnostic features and treatment.

Key words: Glucocorticoid, myopathy, steroid

Introduction

Glucocorticoid-induced myopathy was first described by Harvey Cushing in 1932 in Cushing's syndrome.[1] He noted that patients with endogenous glucocorticoid excess developed severe proximal muscle wasting and weakness. Around 60% of the patients with Cushing's syndrome develop muscle weakness.[2] With increasing use of glucocorticoids to treat several medical conditions, exogenous glucocorticoids have become the most common cause of drug-induced myopathy.[3] Although any commonly used glucocorticoid can cause myopathy, it is implicated more often with the fluorinated glucocorticoid preparations, such as dexamethasone, triamcinolone, and betamethasone.[4] Improvement in muscle weakness is observed when converted to equivalent anti-inflammatory dose of another steroid.[4]

Pathophysiology

Glucocorticoids alter protein metabolism. They decrease the rate of protein synthesis leading to muscle atrophy, but the main effect is to induce muscle protein catabolism.[3] In experimental data from rat studies, muscle atrophy resulted mainly from increased protein breakdown in adult rats, and depressed protein synthesis in aged animals.[5]

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Type of muscle fibers affected

Glucocorticoid-induced muscle atrophy affects fast-twitch glycolytic muscle fibers (type II muscle fibers). Predominantly IIb fibers are affected, whereas less or no impact is observed on type 1 (oxidative) fibers.[6] The mechanism of such fiber specificity is not known. Type IIb fibers are less frequently active than type IIa or type I fibers, and the differences in normal activity patterns may contribute to the greater steroid-induced atrophy of type IIb fibers.[7]

Mechanism of muscle proteolysis

The catabolic effect of glucocorticoids on muscle proteolysis results from the activation of the major cellular proteolytic systems,[8] namely

a. The ubiquitin-proteasome system (UPS)
b. The lysosomal system (cathepsins)
c. The calcium-dependent system (calpains).

Primarily, myofibrillar proteins are degraded. The ubiquitin-proteasome system is considered to play a major role in the catabolic action of glucocorticoids.[6] The UPS does not degrade the intact myofibrils directly. It is thought that actin and myosin are dissociated probably by calpains, before they can be degraded by the UPS.[9]

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Mechanism of inhibition of muscle protein synthesis

There are mechanisms proposed on inhibitory effects of glucocorticoids on protein synthesis.

a. First, glucocorticoids inhibit the transport of amino acids into the muscle, which could limit the protein synthesis[10]
b. Secondly, glucocorticoids inhibit the stimulatory action of insulin, insulin-like growth factor-1, and amino acids (leucine in particular) on the phosphorylation of two key factors (4E-BP1 and S6K1). These two factors play a key role in the protein synthesis machinery by controlling the initiation step of mRNA translation[11,12]
c. Thirdly, there is evidence that glucocorticoids cause muscle atrophy by inhibiting myogenesis through the down-regulation of myogenin, a transcription factor mandatory for differentiation of satellite cells into muscle fibers.[13]

Other proposed mechanisms for muscle atrophy

a. Glucocorticoids can also cause muscle atrophy by altering the production of growth factors that control locally the muscle mass development. They inhibit the production of IGF-1 by muscle. IGF-1 stimulates the development of muscle mass by increasing protein synthesis and myogenesis while decreasing proteolysis and apoptosis. Glucocorticoids also stimulate production of myostatin by the muscles. Myostatin inhibits the muscle mass development by down-regulating the proliferation and differentiation of satellite cells and protein synthesis. For these reasons, decreased muscle IGF-1 and increased muscle myostatin play a key role in glucocorticoid-induced muscle atrophy[6]
b. Another mechanism of glucocorticoid-induced myopathy is mitochondrial dysfunction. The mitochondria are enlarged or aggregated, and their oxidative capacity is decreased due to glucocorticoids action[14]
c. Glucocorticoids also produce muscle weakness by lowering serum potassium and phosphate.[4]

In cases of Endogenous Cushing's syndrome, elevated levels of ACTH may also be myopathic. Excessive amounts of ACTH can impair neuro-muscular transmission by decreasing the quantal content of the end-plate potential. The ACTH excess, therefore, may have myopathic actions that are separate from those of glucocorticoids.[4]

Hypokalemic myopathy is induced by glucocorticoids with high mineralocorticoid activity. Glucocorticoids produce transient hypophosphatemia due to increased renal clearance of phosphate, and severe phosphate depletion can result in muscle necrosis. However, potassium and phosphate depletion do not play an important role in steroid myopathy.[4]

Clinical Presentation

Cushing first noted that patients with endogenous glucocorticoid excess developed proximal muscle wasting and weakness.[1] Severe muscle weakness is found in 2.4% to 21% of patients with exogenous glucocorticoid administration.[15] Actual incidence of steroid-induced weakness is high if mild cases also included.[15] Some individuals are more predisposed like elderly, patients with cancer, with diseases that affect the respiratory muscles, patients with negative nitrogen balance before the initiation of glucocorticoid treatment, and patients who are physically inactive.[16]

Glucocorticoid-induced myopathy can occur in an acute or chronic form. The acute form most often occurs in the intensive care unit setting. It is characterized by rapidly progressive weakness of the proximal and distal muscle groups.[17] Many of these patients are on mechanical ventilation and have received neuromuscular blockade. Immobility, curare-like agents for neuromuscular blockade, high dose of steroid, nutritional deficiencies, and concurrent sepsis contribute to the rapid onset of weakness and wasting, sometimes referred to acute illness myopathy.[15] In chronic myopathy, muscle weakness develops insidiously, progresses slowly, and is usually painless or mildly painful.[3,15] Weakness is primarily proximal; pelvic girdle muscles are more severely involved than arms; and cranial nerve innervated muscles and sphincters are spared. Rarely, the distal muscles are affected.[3,15] Chronic myopathy can lead to muscle atrophy that regresses only after a matter of weeks or months.[17] The pattern of muscle involvement is same in patients with iatrogenic steroid myopathy and endogenous glucocorticoid excess.[15] Patients who have received steroids for less than 4 weeks rarely develop steroid myopathy, although there are wide variations in the dose and duration of steroid treatment associated with glucocorticoid-induced myopathy.[18] The use of prednisone or equivalent drugs in doses of lower than 10 mg/day are rarely associated with glucocorticoid-induced myopathy; higher glucocorticoid doses result in more rapid onset of clinically significant muscle weakness, which can be observed within 2 weeks after the initiation of corticosteroid therapy; the use of prednisone or equivalent drugs in doses of 40-60 mg/day for at least 1 month results in some degree of muscle weakness.[16] Treatment with non-fluorinated glucocorticoids, especially methylprednisolone, has been shown to cause acute muscle weakness in situations of stress, such as acute spinal cord injury or acute respiratory

distress syndrome. Inhaled corticosteroids are rarely associated with myopathy; if such myopathy occurs, it can be quickly reversed by interrupting the steroid treatment.[3]

Table 1: Summary of Glucocorticoid induced myopathy

General	• Seen in both endogenous hypercortisolism as well as exogenous glucocorticoid administration. • More common with fluorinated glucocorticoid preparations, such as dexamethasone, triamcinolone, and betamethasone • Patients who have received steroids for less than 4 weeks rarely develop steroid myopathy. • Mainly Type IIb muscle fiber atrophy is seen
Mechanisms	A. Increased protein breakdown and decreased protein synthesis A.1 Increased protein breakdown pathways a) Ubiquitin-proteasome system (UPS) b) Lysosomal system (cathepsins) c) Calcium-dependent system (calpains) A.2 Decreased protein synthesis a) Inhibition of transport of amino acids into the muscle b) Inhibition of the stimulatory action of insulin, insulin-like growth factor-1, and amino acids on the phosphorylation of two key factors involved in controlling the initiation step of mRNA translation) c) Inhibition of myogenesis through down-regulation of myogenin B. By changes in the production of two growth factors, which control muscle mass, namely IGF-1 and myostatin C. By causing mitochondrial dysfunction D. By lowering serum potassium and phosphate
Clinical presentation	Can occur in an acute or chronic form • The acute form of glucocorticoid-induced myopathy most often occurs in the intensive care unit setting • It is characterized by rapidly progressive weakness of the proximal and distal muscle groups • In chronic form, weakness is primarily proximal, with pelvic girdle muscles more severely involved than the arms. • Cranial nerve innervated muscles and sphincters are spared
Predisposed individuals	• Some individuals like elderly, patients with cancer, patients with diseases that affect the respiratory muscles, patients with negative nitrogen balance before the initiation of glucocorticoid treatment, and patients who are physically inactive are more predisposed
Predisposing conditions	• Immobility, curare-like agents for neuromuscular blockade, high dose of steroid, nutritional deficiencies, and concurrent sepsis
Lab diagnosis	• Lactate dehydrogenase (LDH), creatine kinase, and aldose are usually normal • On electromyography, a myopathic pattern is observed in the later stages • Histologic studies on muscle biopsy reveals non-specific atrophy of type IIb muscle fibers, absence of inflammatory infiltrate
Treatment	• Reducing steroid dose, alternate day treatment regimen, and switching to a non-fluorinated glucocorticoid preparation • Good protein diet and physical activity • Experimental treatments that have been used in glucocorticoid-induced myopathy are IGF-1, branched-chain amino acids, creatine, androgens, and glutamine

Diagnostic Evaluation

The diagnostic approach to patient with glucocorticoid-induced myopathy involves evaluation for endogenous hypercortisolism or exogenous glucocorticoid use. Serum levels of muscle associated enzymes like creatine kinase, lactate dehydrogenase (LDH), and aldose are usually normal. However, in acute phase, the levels of creatine kinase and aldose may be quite high.[3,15] On electromyography (EMG), a myopathic pattern is observed in the later stages. EMG results are typically normal in the early stages of the disease.[4] Histologic studies on muscle biopsy reveals non-specific atrophy of type IIb muscle fibers, absence of inflammatory infiltrate, variations in fiber size with centrally placed nuclei, and rarely signs of muscle necrosis.[3]

Treatment

The treatment of underlying etiology for glucocorticoid excess state is important. For exogenous cause, reducing steroid dose, alternate day treatment regimen, and switching to a non-fluorinated agent are associated with improvement in muscle weakness.[15] An increase in muscle strength can be observed within 3 to 4 weeks after discontinuation of the glucocorticoid. An adequate protein intake is helpful in preventing rapid acceleration of symptoms.[15] Physical therapy may be useful in preventing and treating muscle weakness in patients receiving glucocorticoids.[19,20] Some of the experimental treatments that have been used in glucocorticoid-induced myopathy are IGF-1, branched-chain amino acids, creatine, androgens, and glutamine.[3,6]

The summary of the review is tabulated in Table 1.

References

1. Cushing H. The basophil adenoma of the pituitary body and their clinical manifestation. Johns Hopkins Med J 1932;50:137.
2. Stewart PM, Krone NP. The Adrenal Cortex. In: Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, editors. Williams Textbook of Endocrinology. Philadelphia: Elsevier Saunders; 2011. p. 479-544.
3. Pereira RM, Freire de Carvalho J. Glucocorticoid-induced myopathy. Joint Bone Spine 2011;78:41-4.
4. Anagnos A, Ruffi RL, Kaminski H. Endocrine myopathies. Neurol Clin 1997;15:673-96.
5. Dardevet D, Sornet C, Savary I, Debras E, Patureau-Mirand P, Grizard J. Glucocorticoid effects on insulin- and IGF-I-regulated muscle protein metabolism during aging. J Endocrinol 1998;156:83-9.
6. Schakman O, Gilson H, Thissen JP. Mechanisms of glucocorticoid-induced myopathy. J Endocrinol 2008;197:1-10.
7. DuBois DC, Almon RR. Disuse atrophy of skeletal muscle is associated with an increase in number of glucocorticoid receptors. Endocrinology 1980;107:1649-51.

8. Hasselgren PO. Glucocorticoids and muscle catabolism. Curr Opin Clin Nutr Metab Care 1999;2:201-5.
9. Hasselgren PO, Fischer JE. Muscle cachexia: Current concepts of intracellular mechanisms and molecular regulation. Ann Surg 2001;233:9-17.
10. Kostyo JL, Redmond AF. Role of protein synthesis in the inhibitory action of adrenal steroid hormones on amino acid transport by muscle. Endocrinology 1966;79:531-40.
11. Shah OJ, Kimball SR, Jefferson LS. Acute attenuation of translation initiation and protein synthesis by glucocorticoids in skeletal muscle. Am J Physiol Endocrinol Metab 2000;278:E76-82.
12. Shah OJ, Kimball SR, Jefferson LS. Among translational effectors, p70S6k is uniquely sensitive to inhibition by glucocorticoids. Biochem J 2000;347:389-97.
13. te Pas MF, de Jong PR, Verburg FJ. Glucocorticoid inhibition of C2C12 proliferation rate and differentiation capacity in relation to mRNA levels of the MRF gene family. Mol Biol Rep 2000;27:87-98.
14. Mitsui T, Azuma H, Nagasawa M, Iuchi T, Akaike M, Odomi M, *et al*. Chronic corticosteroid administration causes mitochondrial dysfunction in skeletal muscle. J Neurol 2002;249:1004-9.
15. Alshekhlee A, Kaminski HJ, Ruff RL. Neuromuscular manifestations of endocrine disorders. Neurol Clin 2002;20:35-58.
16. Miller ML. Glucocorticoid-induced myopathy. Up to Date, version 16.3, 2009.
17. Van Balkom RH, van Der Heijden HF, van Herwaarden CL, Dekhuijzen PN. Corticosteroid induced myopathy of the respiratory muscles. Neth J Med 1994;45:114-22.
18. Askari A, Vignos PJ Jr, Moskowitz RW. Steroid myopathy in connective tissue disease. Am J Med 1976;61:485-92.
19. Braith RW, Welsch MA, Mills RM Jr, Keller JW, Pollock ML. Resistance exercise prevents glucocorticoid-induced myopathy in heart transplant recipients. Med Sci Sports Exerc 1998;30:483-9.
20. La Pier TK. Glucocorticoid-induced muscle atrophy. The role of exercise in treatment and prevention. J Cardiopulm Rehabil 1997;17:76-84.

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