

# Glucocorticoid-Induced Myopathy: Typology, Pathogenesis, Diagnosis, and Treatment

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## ABSTRACT

Glucocorticoid-induced myopathy is a non-inflammatory toxic myopathy typified by proximal muscle weakness, muscle atrophy, fatigue, and easy fatigability. These vague symptoms coupled with underlying disorders may mask the signs of glucocorticoid-induced myopathy, leading to an underestimation of the disease's impact. This review briefly summarizes the classification, pathogenesis, and treatment options for glucocorticoid-induced muscle wasting. Additionally, we discuss current diagnostic measures in clinical research and routine care used for diagnosing and monitoring glucocorticoid-induced myopathy, which includes gait speed tests, muscle strength tests, hematologic tests, bioelectrical impedance analysis (BIA), dual-energy X-ray absorptiometry (DXA), computed tomography (CT), magnetic resonance imaging (MRI), electromyography, quantitative muscle ultrasound, histological examination, and genetic analysis. Continuous monitoring of patients receiving glucocorticoid therapy plays an important role in enabling early detection of glucocorticoid-induced myopathy, allowing physicians to modify treatment plans before significant clinical weakness arises.

## Introduction

Skeletal muscles account for 40–50% of the human body and play a crucial role in metabolism, energy expenditure, physical strength, and movement activities. The dynamic balance between muscle fiber biosynthesis and degradation determines the level of muscle mass. Any factor that disrupts this balance may lead to a decrease or atrophy of muscle mass, usually caused by protein degradation from various pathological and physiological factors [1, 2]. Elevated circulating glucocorticoids (GCs) levels may be one of the trig-

gering factors in many pathological conditions characterized by muscle atrophy, such as sepsis, cachexia, starvation, metabolic acidosis, and severe insulin deficiency. Other factors, including malnutrition, increased cytokine production, and long-term bed rest, may also result in muscle wasting in these pathological conditions. Research has shown that adrenal gland removal or treatment with GCs receptor antagonists can alleviate muscle atrophy, indicating that excessive GCs are one of the causes of muscle loss [3].

GCs-induced myopathy, a non-inflammatory toxic myopathy, is the most common drug-induced myopathy and was first described by Harvey Cushing in 1932 [4]. It is typically caused by endogenous or exogenous excess of GCs. Data shows that 50–80% of patients with Cushing syndrome (CS) present with muscle weakness [5] and up to 50% of patients on long-term GCs treatment develop myopathy [6]. Due to the nonspecific symptoms associated with muscle involvement, GCs-induced myopathy is often underestimated and overshadowed by the underlying disease of the patient [7]. Clinical features of this condition include proximal muscle weakness, muscle wasting, fatigue, and easy fatigability [5, 8]. GCs-induced myopathy mainly affects the proximal symmetric muscles of the lower limbs, with significant involvement of the postural muscles [8]. Patients may gradually lose the ability to stand up from a low chair, climb stairs, and ultimately perform activities of daily living, with significant atrophy of the surrounding muscles also being observed. Generalized weakness and mental fatigue are also common symptoms associated with this condition [5]. Research has shown that GCs-induced myopathy primarily affects fast-twitch fibers (type II fibers), especially type IIb fibers, with type I fibers being largely unaffected [3]. The mechanism of this fiber type specificity is unclear, but it may be related to differences in normal activity patterns between different fiber types, leading to greater susceptibility of type IIb fibers to atrophy induced by GCs [9].

## GCs-Induced Myopathy Typology

GCs-induced myopathy can be divided into acute and chronic categories [10]. Acute GCs-induced myopathy is frequently observed in the intensive care unit (ICU), particularly when administered intravenously at high doses [11]. This form presents early in treatment as rapidly progressive weakness in both proximal and distal muscle groups and may involve respiratory muscles [10]. Clinical features include generalized muscle weakness, rhabdomyolysis, extreme myasthenia, inhibited or absent muscle stretch reflexes, flaccid tetraplegia, intact sensitivity, and cranial nerve dysfunction [5]. Serum levels of myosin and aldolase vary from normal to significantly elevated, electromyography displays myopathic motor unit potentials and recruitment, while muscle biopsy often shows type I and type II fibers atrophy and necrosis [11].

Chronic atrophic GCs-induced myopathy affects up to 60% of patients on chronic GCs therapy [12], with higher incidence rates noted with fluorinated GCs preparations [13]. This form progresses slowly as muscle weakness and atrophy manifest mostly in the proximal muscles, especially those in the pelvic region. Notably, distal muscles are rarely involved, and pain is minimal or absent [14]. Serum levels of myosin and aldolase are below normal, while electromyography typically shows small polyphasic potentials without spontaneous insertional activity. Administering GCs below 10 mg/day is rarely linked with their induced myopathy; however, doses of 40–60 mg/day for at least one month can cause varying degrees of muscle weakness [9]. Therefore, meticulous monitoring of dose and duration is necessary during GCs therapy to avoid serious myopathic complications [15]. Furthermore, the severity and underlying mechanism of chronic catabolic effects may vary with age; studies have established that GCs-induced muscle atrophy is markedly more severe in elderly rats than in their young counterparts [16].

## Pathogenesis Mechanism

The precise molecular mechanisms underlying GCs-induced muscle atrophy have yet to be fully elucidated [17]; however, reductions in protein synthesis and elevations in protein degradation through various molecular pathways are believed to contribute to its pathogenesis. Notably, the inhibitory effect of GCs on p70 ribosomal S6 protein kinase (p70S6K) is thought to disrupt protein synthesis machinery and promote atrophy [18]. Simultaneously, activation of the ubiquitin-proteasome system and lysosomal system are postulated to enhance muscle proteolysis and breakdown, with identified genes such as Atrogin-1, MuRF-1, Cathepsin-L, PDK4, p21, Gadd45, and 4E-BP1 functioning in mediating these processes [19, 20].

Moreover, insufficiencies involving insulin-like growth factor 1 (IGF-1) are believed to foster GCs-induced muscle atrophy [8]. IGF-1 activates the phosphatidylinositol-3-kinase/Akt pathway, which blocks GCs action and prevents muscular atrophy [17]. Conversely, reductions in IGF-1 expression compromise this protective mechanism. Furthermore, overexpression of myostatin (MSTN), a growth factor originating in skeletal muscles that inhibits muscle mass growth and leads to muscle cell atrophy by repressing satellite cells and protein synthesis, exacerbates this form of muscle atrophy [21]. Both augmented IGF-1 expression and deletion of the myostatin gene have been used successfully in animal models to prevent GCs-induced muscle atrophy, suggesting potential therapeutic approaches for preventing or treating this disorder [22].

Summarily, molecular mechanisms involving decreased protein synthesis, increased protein degradation, decreased IGF-1, increased MSTN, and regulation of related gene expression are implicated in GCs-induced muscle atrophy. Targeting these mechanisms, stimulating IGF-1, and inhibiting MSTN could become promising therapeutic approaches. A more comprehensive understanding of molecular mechanisms surrounding this disorder may offer insights into its pathogenesis and guide the development of effective therapeutic strategies.

## Diagnostic Measures

### Gait Speed Test

The gait speed test is an essential tool for evaluating one's degree of deterioration in gait ability, with the 6-minute and 10-meter tests serving as the primary methods for assessment. The former necessitates adequate space and involves walking as quickly as possible around a marked loop while receiving scores at each lap. After six minutes, participants stand sideways and alternate leg lifts [23]. Conversely, the 10-meter test assesses an individual's average step speed over a fixed distance through a ten-meter linear route with demarcated start and endpoints. Once underway, timing starts upon signal, and the timekeeper records both the time taken and the number of steps. Testing is performed three times, following which an average score is computed [24]. Using the cut-off point  $<0.8$  m/s defined by the European Working Group on Sarcopenia in the Elderly (EWGSOP) guidelines identifies patients with low physical function [25].

Assessing gait speed in patients undergoing GCs therapy can anticipate their health status and future functional decline risks.

Moreover, gait speed is an important clinical indicator for evaluating physical function and daily living abilities for individuals struggling with musculoskeletal system disorders or those who are elderly or disabled. Consequently, the gait speed test warrants consideration as a straightforward yet effective clinical assessment instrument [23].

## Muscular Strength Testing

Muscle strength testing is an essential tool for assessing muscular power through both semi-quantitative and quantitative techniques. The former relies on manual muscle testing, providing subjective ratings of muscle strength with some degree of error occasionally seen [26]. However, semi-quantitative assessments can still be useful in select cases. Alternatively, quantitative assessment evaluates direct quantitative measurements such as grip strength testing, which offers reliable data output. Grip strength tests typically entail a standardized evaluation format using the right or dominant hand – or both sides – of the patient. The test involves sitting up straight with their elbow bent at 90° while maintaining their grip continuously for at least 3 seconds, with a pause of 30 seconds between each attempt. The highest value recorded after three attempts represented the final record [27–29]. A cut-off point of < 30 kg for men and < 20 kg for women identified low grip strength patients. Grip strength testing remains one of the simplest and recommended methods to assess muscle strength and exhibits strong correlation values with lower limb muscle strength [30], while its normative data supports identifying weakness with high-reliability indices.

In GCs-induced myopathy, muscle strength testing facilitates early diagnosis to determine potential intervention strategies possible consequently reducing health risks. In a longitudinal prospective study examining the long-term prognosis of CS-associated myopathies, muscle function was assessed based on hand grip strength and chair rise capacities [31]. Muscle dysfunction has been discovered to persist even after hormone levels return to normal. Therefore, muscle strength testing remains a valuable modality for identifying potential candidates for intervention to mitigate significant health hazards [23]. In clinical practice, muscle strength assessment remains a rapid and straightforward method and serves as an excellent tool to identify and diagnose skeletal muscle atrophy and is considered potentially crucial for accurate diagnosis and treatment of conditions involving diminished muscle strength [32]. However, it is crucial to recognize that the results of muscle strength assessments can be influenced by multiple factors such as age, gender, and other medical conditions; hence, requiring extensive analysis before implementation [23].

## Hematological Examination

The hematological examination has been increasingly utilized in GCs-induced myopathy diagnosis, involving the analysis of various biomarkers such as creatine kinase (CK), myoglobin, aldolase, transaminase, and lactate dehydrogenase. Elevated levels of both CK and aldolase may occur in patients with acute or severe GCs-induced myopathy [13]. However, they are frequently observed to be within reference ranges, limiting their diagnostic utility for chronic GCs-induced myopathy identification. Additionally, a combined assessment of serum CK and urine creatinine may offer lim-

ited support, even though it may prove beneficial, particularly when normal levels of serum CK and raised urine creatinine suggest the presence of chronic GCs-induced myopathy. Nevertheless, the combined testing approach is restricted in patients presenting with impaired renal function, where urinary creatinine excretion may indicate the early onset of myopathy and be more common during GCs therapy [5].

In a single-blind placebo-controlled study of twenty participants receiving short-term dexamethasone, enhanced muscle strength and decreased circulating muscle protein levels such as CK and myoglobin were observed – yet these remained within normal reference ranges [33]. Khaleeli et al. [34] reported decreased CK levels in lateral femoral muscle biopsies of CS patients, suggesting a potential contribution to the observed reduction in serum CK levels. Indeed, the hematological examination can showcase some significance in diagnosing GCs-induced myopathy. However, conventional parameters' diagnostic value remains poor, especially for diagnosing chronic GCs-induced myopathy.

## Bioelectric Impedance Analysis

Bioelectrical impedance analysis (BIA) is a valuable tool for assessing changes in muscle mass and body composition in individuals with GCs-induced myopathy. However, it cannot be used as a sole diagnostic method. BIA utilizes the skeletal muscle mass index (SMI) to measure muscle mass across different body segments [23]. Additionally, BIA infers body composition by analyzing electrical conductivity, which provides insight into variables such as body fat content and overall water content [35]. Therefore, regular use of BIA can help monitor changes in body composition and muscle mass in patients with GCs-induced myopathy, providing insights that can guide timely adjustments to their treatment plans [36]. Though BIA has become widely applied as a tool for muscle mass assessment and monitoring, limited research exists regarding its utility in tracking muscle changes associated with GCs-induced myopathy [37]. While some studies suggest that bioelectrical impedance analysis may detect changes in muscle mass, further validation and confirmation are necessary. Consequently, alternative methods remain critical for assessing muscle changes associated with GCs-induced myopathy. Researchers must also ensure the appropriate selection of equipment and validation and calibration of their test populations when utilizing BIA during muscle mass assessment in patients with this condition.

## Dual-Energy X-ray Absorption

Dual-energy X-ray absorptiometry (DXA) is a technique for assessing body composition, including muscle and adipose tissue content. The method measures differences in X-ray absorbance rates in various body tissues to determine the relative proportions of different components [38]. When detecting skeletal muscle and adipose tissue, changes in hydration are used to infer changes in lean tissue attenuation of X-rays in the body [39]. While DXA can detect the overall content of lean tissue, some of these percentages include non-muscle components such as connective or fibrous tissue, water, and organic mass – rather than solely representing skeletal muscle mass [40].

GCs-induced myopathy is characterized by muscle atrophy and fat accumulation. Thus, DXA technology plays a valuable role in

monitoring changes in patients' muscle mass and adipose tissue content over time, providing crucial information for clinicians treating this disease [41]. Additionally, DXA assessment can be employed to diagnose bone density problems like osteoporosis and reduced bone mass and monitor changes in patients' body composition caused by medical intervention [42]. These assessments enable physicians to adjust treatment, accordingly, optimizing patient care.

## Computed Tomography

Computed tomography (CT) can be employed to assess muscle atrophy resulting from skeletal muscle loss in patients with GCs-induced myopathy. In these patients, CT determines the cross-sectional area (CSA) of the muscle by measuring the muscle area at the caudal level of the third lumbar vertebra [43] or other relevant reference points [44]. In animal experiments, CT has been used to assess muscle mass before and after the administration of GCs, with results showing significant reductions in CSA of muscles at the paraspinal level of the third lumbar vertebra and the mid-femur following GCs administration [45]. In humans, CT has similarly been applied to assess muscle atrophy caused by various diseases, with resultant ACT scans revealing substantial losses in muscle mass in regions such as the thigh, abdomen, and paravertebral canal due to either endogenous or exogenous GCs [46–48].

Studies have shown that CT is a more precise estimator of skeletal muscle loss than BIA in patients with GCs-induced myopathy, yet despite the accuracy of CT assessments, its clinical application remains limited due to equipment complexity, high costs, and low availability, as well as the risk of radiation exposure [49]. Consequently, CT currently has not been incorporated widely in the daily clinical practice for patients with this condition.

## Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) enables the assessment of muscle structure, size, thickness, and volume, offering advantages over other imaging techniques due to its ability to generate high-resolution images without ionizing radiation [50]. Chemical shift imaging and Dixon-based T2W imaging, in particular, represent new tools for assessing fat infiltration [51]. Through MRI signal analysis, it is possible to measure the specific fat and water-based properties of muscle [50, 52], detect the presence of intramuscular lipids [53], and assess changes in both edema and mitochondrial metabolism [54].

T1-weighted MRI provides high-resolution anatomical images that showcase unique features of muscle-fat replacement, whereas T2-weighted sequences are best employed for detecting acute pathology or changes, such as inflammation, edema, or changes characterized by increased blood flow. Despite similarities between ultrasound and MRI results when measuring muscle thickness, MRI uniquely offers the ability to measure the cross-sectional area and volume of larger muscles with relative ease, making it a useful tool for monitoring changes in muscle composition [55, 56]. Nonetheless, ultrasound remains more appropriate for tracking intramuscular fibrosis [57, 58].

## Electromyography

Electromyography (EMG) permits the identification of muscle abnormalities – such as weakness, atrophy, and slowed fiber conduction velocity (MFCV), which are often associated with GCs-induced myopathy. EMG records the electrical activity of muscle fibers through the insertion of needle electrodes into the muscle [7]. Research by Minetto et al. [7] suggests that slowed MFCV may have a connection to GCs-induced myofiber atrophy in patients with Cushing's disease, while other studies indicate that healthy individuals receiving dexamethasone for short periods may experience impaired muscle function characterized by significantly lower MFCV and electromyographic fatigue performance compared to controls [33]. While the MFCV changes associated with GCs-induced myopathy suggest that they represent a sensitive marker of impaired muscle function [59], research by Blijham et al. [60] found that EMG MFCV values depend primarily on muscle fiber diameter as opposed to underlying neuromuscular disease.

In chronic GCs-induced myopathy, EMG readings typically appear normal, with only a small portion of patients exhibiting minor electrophysiological dysfunction [60]. Therefore, EMG cannot be relied upon solely to diagnose GCs-induced myopathy and should be complemented by other clinical, imaging, or laboratory findings [10]. Nonetheless, EMG remains one of the most important tools available for diagnosing myopathies and identifying abnormalities in muscle electrical activity. As such, it can provide valuable information to assist physicians in making accurate diagnostic and treatment decisions.

## Quantitative Muscle Ultrasound

Muscle ultrasound is extensively employed in the screening and evaluation of neuromuscular diseases to identify fat replacement and fibrosis in affected muscles using ultrasound [61]. As opposed to conventional muscle examination techniques, muscle ultrasound technology provides a noninvasive, patient-friendly approach that enables immediate neuromuscular imaging [62]. Furthermore, quantitative muscle ultrasound (QMUS) echo analysis allows for a more sensitive and effective differentiation between healthy and diseased muscles. This technique permits the assessment of parameters such as muscle thickness and structure (e. g., fascicle length and pennation angle) [63], in addition to quantifying muscle echo intensity related to the fibrous and adipose tissue content of the muscle [61].

In GCs-induced myopathy, muscle structure alterations occur as healthy muscle fibers become diseased, atrophy, and are replaced by adipose and fibrotic tissue [64]. The interplay between muscle and fat as well as fibrosis results in multiple tissue/sound velocity transitions that transmit ultrasound signals back to the transducer, increasing echo intensity. Structural changes in the muscle caused by fibrosis and steatosis lead to increased echo intensity, affecting tissue elasticity and muscle anisotropy [65]. As the disease progresses, the ultrasound presentation of GCs-induced myopathy becomes increasingly abnormal, with identifiable muscle structure loss and escalating echo intensity of ultrasound images [64]. QMUS holds great promise as an important tool for diagnosing and evaluating GCs-induced myopathy.

The QMUS method for assessing muscle echoes primarily employs grayscale analysis and reference values. Muscle echoes can

be efficiently quantified using image software capable of acquiring regions of muscle interest and determining the average grayscale of the region (0–255) using a histogram function [66]. The overall detection rate of neuromuscular diseases has been reported to exceed 90% [67]. It is crucial to acknowledge that the limitation of muscle echo intensity assessment is the significant impact of ultrasound examination on the operator, operating technique, and transducer probe position and angle relative to the tissue [68]. For optimal results, it is recommended to use a standardized imaging protocol and patient positioning, keep the transducer perpendicular to the tissue, utilize ample transducer gel and soft touch to minimize tissue compression, ensure muscles are relaxed, support the patient's extremities on the examination table or pillow, and perform both transverse and longitudinal axial directions.

Few studies have employed QMUS as a research tool for evaluating muscle mass in patients with GCs-induced myopathy. Minetto et al. [69] initially described the feasibility and validity of QMUS in assessing GCs-induced changes in the mass and structure of skeletal muscle in the extremities. The study discovered that half of the patients with Cushing's disease exhibited muscle mass impairment, with a more pronounced reduction in proximal muscle thickness. Muscle echogenic intensity was significantly negatively correlated with muscle functional assessment [63]. Martucci et al. [70] evaluated QMUS results in patients receiving dexamethasone for brain tumors and identified an increase in muscle echo intensity corresponding to increasing treatment duration. These studies preliminarily suggest that muscle echo intensity may predict muscle dysfunction in patients with GCs-induced myopathy and monitor the progression of the myopathic process over time [71]. Distinguishing between underlying disease activity and drug-induced muscle weakness in patients with active myositis treated with high doses of GCs who develop worsening proximal muscle weakness can be diagnostically challenging. In these cases, clarifying the role of QMUS requires further comparison of ultrasound findings in patients with active myositis and those treated with high-dose GCs.

Treating GCs-induced myopathy is challenging, as patients are often initially diagnosed with associated muscle damage [31]. QMUS enables screening for GCs-induced myopathy before symptom onset and avoids more invasive tests [64]. While QMUS has the potential to serve as a valuable diagnostic tool for GCs-induced myopathy, additional studies are required to confirm its worth.

## Histopathological Examination

Histopathology is utilized in the evaluation of numerous neuromuscular diseases. This method enables the identification of muscle fiber atrophy, necrosis, inflammation, and other abnormalities associated with GCs-induced myopathy. Although not mandatory for diagnosis, histopathology has been employed extensively in various studies to analyze pathological and phenotypic changes resulting from exogenous and endogenous GCs overdoses [5, 34]. These changes primarily involve ultrastructural alterations in myofibrils and mitochondria, particularly in type II fibers, as evidenced by splitting and disorganization of myofibrils, selective loss of thick myosin filaments, retention of Z-bands, mitochondrial ridge disruption, and aggregation between myofibrils and among myogenic fibers. Other notable changes are the appearance of large heteromorphic mitochondria, an increase in vacuoles between myofi-

brils, and an elevation in sarcoplasmic glycogen and lipid content [5]. Furthermore, significant changes in muscle phenotype, including shifts in the distribution of myosin-heavy chains between fast and slow types, have been observed in both human and animal models [72, 73]. Minetto et al. [74] demonstrated that short-term GCs treatment induces quantitative and qualitative adaptations through histopathological examination in healthy participants, manifesting as atrophy of IIa and IIx fibers, cross-sectional area diminution, and decreased myosin concentration. Hence, it is critical in practice to minimize the dose and duration of treatments to prevent or reduce adverse effects. While histopathology is frequently used to investigate GCs-induced changes in muscle protein metabolism, it is limited to clinical studies and cannot be utilized as a routine patient assessment tool [33]. Therefore, identifying easily evaluable biomarkers of metabolic damage in muscle tissue holds significant clinical value.

## Genetic Analysis

Recent investigations have revealed that variations in genotyping could influence an individual's susceptibility to GCs, suggesting that genotyping could assist in personalizing medications. A case of simultaneous osteonecrosis and severe GCs-induced myopathy was reported by West China Hospital of Sichuan University [75]. Magnetic resonance imaging (MRI) of the patient displayed osteonecrosis in both legs, specifically in the femoral head, distal femur, and proximal tibia. Additionally, a biopsy of the right quadriceps muscle exhibited type II muscle fiber atrophy without leukocyte infiltration, indicative of GCs-induced myopathy.

Genetic analysis demonstrated that the patient possessed a 5G/5G genotype of the PAI-1 gene, which is associated with increased muscle inflammation and impaired muscle regeneration, thus promoting muscle atrophy and fibrosis [76]. The 4G/4G allele of PAI-1 has been linked to a heightened risk of osteonecrosis compared to the 5G/5G allele [77]. Furthermore, the ABCB1 gene (C3435T) exhibited a C/C genotype, which is correlated with an elevated risk of osteonecrosis relative to the TT and TC genotypes of the same gene. The ABCB1 gene encodes the transporter protein p-glycoprotein (P-gp), which is essential for expelling foreign substances from cells [75]. Polymorphisms within the ABCB1 gene that result in diminished P-gp expression or dysfunction have also been implicated in drug-induced myopathy.

This patient's genetic profile suggested a heightened sensitivity to GCs, and a subsequent reduction in adverse events was observed as the GCs dosage was gradually decreased [75]. Genotyping may prove beneficial for patients undergoing specific treatments that are known to cause severe side effects in susceptible individuals. As such, it is recommended that frequent GCs users or those experiencing serious adverse events undergo genotyping for GCs side effect risk genes. This could inform decisions regarding GCs dose reduction or alternative treatments. However, the practicality and cost-effectiveness of this approach require further investigation.

## Interventions

Minetto et al. [63] discovered that in patients with Cushing's syndrome, muscle mass takes longer to recover than muscle structure after relief from the hypercortisolemia state. Even with biochemi-

► **Table 1** Studies of different diagnostic examinations in patients with glucocorticoid-induced myopathy.

Diagnostic examinations	Investigators [Ref] and Study Design	Publication year	Number of cases	Comparator	Findings
Gait Speed Test	Minetto MA et al. [63]	2019	33	13 remitted CS patients	The two groups of patients showed comparable values of walking speed ( $p=0.43$ )
	Retrospective observational study				
Muscular Strength Testing	Vogel F et al. [31]	2020	88	29 rule-out CS patients	Grip strength temporarily worsens during steroid withdrawal and remains impaired in long-term follow-up ( $p<0.001$ )
	Prospective observational study				
Hematological Examination	Minetto MA et al. [33]	2010	10	10 healthy control individuals	Serum CK ( $p<0.01$ ) and plasma myoglobin ( $p<0.01$ ) significantly decreased after dexamethasone administration
	Randomized controlled study				
BIA CT MRI	Hosono O et al. [49]	2014	22	None	SMI determined with BIA, mid-thigh muscle CSA on CT or MRI images were negatively correlated with GC dosage ( $p<0.01$ )
	Retrospective observational study				
CT	Nawata T et al. [47]	2018	7	8 patients without myositis	In both groups, the cross-sectional areas of skeletal muscles decreased (myositis group: $p=0.0156$ ; control group: $p=0.0391$ )
	Retrospective observational study				
Electromyography	Minetto MA et al. [33]	2010	10	10 healthy control individuals	The decline of muscle fiber conduction velocity ( $p<0.05$ ) and significant reductions ( $p<0.05$ ) of the myoelectric manifestations of fatigue were observed for biceps brachii, vastus lateralis and medialis, and tibialis anterior muscles
	Randomized, controlled study				
Quantitative Muscle Ultrasound	Minetto MA et al. [63]	2019	33	13 remitted CS patients	The echo intensity of vastus lateralis, tibialis anterior (lower portion), and medial gastrocnemius was significantly ( $p<0.05$ ) higher in patients with active disease compared to patients with the remitted disease
	Retrospective observational study				
Histopathological Examination	Minetto MA et al. [74]	2015	5	None	The percentage decrease in CSA for type IIA fibers was 17% ( $p=0.008$ ) and had a significant loss of myosin after administration ( $p<0.0001$ )
	Intervention study				
Genetic analysis	Hu Y et al. [75]	2022			Genotyping of the patient showed a 5G/5G genotype of the PAI-1 gene and a CC genotype of the ABCB1 gene (C3435T), suggesting she was sensitive to GCs
	Case report				

CS: Cushing's disease; CK: Creatine kinase; BIA: Bioelectric Impedance Analysis; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; SMI: Skeletal muscle mass index; CSA: Cross-sectional area.

cal remission achieved, muscle function may not improve [78], as observed through follow-up studies exhibiting a substantial correlation between the quality of life and muscle function [31]. It underscores the importance of effective interventions to mitigate muscle impairment after achieving biochemical remission. The true risk factors for GCs-induced myopathy are uncertain, leaving treatment reliant on reducing or ceasing GCs use, with particular emphasis on the substitution of fluorinated GCs with non-fluorinated ones at low doses [79]. Fumio Kanda and his team found that growth hormone (GH) alleviates GCs-induced muscle atrophy in rats, mitigating associated urinary metabolic alterations. GH exerts

its effects on muscle cells primarily through the production of IGF-1 in the liver and muscles [80]. Additionally, it was found that creatine supplementation ameliorates muscle mass changes and motor impairment, but has little effect on GCs-induced respiratory pattern changes in animals [81]. However, experimental therapeutic approaches such as GH, IGF-1, and creatine are currently limited to animal experiments, and their feasibility or practicality in clinical practice remains doubtful. Non-pharmacological interventions, including moderate endurance and resistance training [5, 82], mitigate GCs-induced muscle atrophy and weakness, however, high-intensity exercise could be deleterious according to pre-

liminary experimental outcomes [83]. Uchikawa et al. [83] noted increased exercise intensity contribution to muscle weakness and atrophy consequent to intense exercise in rats experiencing GCs-related myopathy. Thus, recommending moderate-intensity exercise training as the preferred intervention to improve muscle function is advised.

A tabular survey of studies of different diagnostic examinations in patients with GCs-induced myopathy is presented in ► **Table 1**.

## Conclusion

Existing diagnostic examinations have limited applicability in the routine evaluation and follow-up of patients with steroid myopathies. Various methods have their scopes and limitations, making it difficult to independently cover all aspects of steroid myopathy assessment. Easily assessable alternative parameters such as walking speed, muscle strength, and circulating muscle protein levels have not demonstrated sufficient diagnostic value in steroid myopathy diagnosis. Future monitoring and diagnostic efforts should not be confined to a single diagnostic method but should comprehensively incorporate various approaches like gait testing, grip strength, hematologic testing, and QMUS to fully understand the dynamic changes in steroid myopathy. Current interventions primarily focus on reducing or discontinuing GCs use. However, the feasibility of other experimental treatments and non-pharmacological interventions remains uncertain. Research on the effectiveness and practicality of musculoskeletal rehabilitation in steroid myopathy patients is insufficient. The impact of exercise intensity on muscle function recovery in steroid myopathy is currently unclear. Given the limitations of diagnostic methods and interventions, future research directions may include improving existing diagnostic methods, exploring new biomarkers, understanding the pathogenesis of steroid myopathy at physiological and molecular levels, conducting large prospective studies to validate and compare the accuracy and feasibility of different diagnostic methods, and enhancing collaboration among various diagnostic methods to improve the effectiveness of comprehensive diagnostic approaches. Through these efforts, a more comprehensive and accurate understanding of steroid myopathy can be achieved, providing more effective methods for future treatment and management.

## Conflict of Interest

The authors declare that they have no conflict of interest.

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