Glucocorticoid-induced myopathy a comprehensive review

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General Medicine

- Glucocorticoid-induced myopathy(GIM) is a common and potentially debilitating complication of prolonged corticosteroid therapy, leading to progressive muscle weakness and atrophy.
- GIM is characterised by proximal muscle weakness, atrophy, persistent fatigue, and reduced muscular endurance , predominantly affecting the lower limbs.
- The pathophysiology involves both **catabolic and anti-anabolic** mechanisms, leading to the degradation of muscle proteins and inhibiting protein synthesis

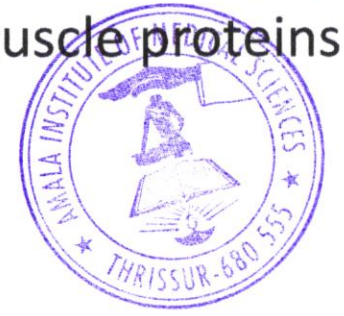


Table 1 Main commonly used corticosteroids and their relative potencies

Type	Duration of action – Biologic Half-life (hours)	Drug	Plasma half-life (minutes)	Routes of administration	Equivalent glucocorticoid dose (mg)*	Relative glucocorticoid potency**	Relative mineralocorticoid potency**
Glucocorticoids	Short-lasting (8-12)	*Cortisol (Hydrocortisone)* Reference	90	O – IV – IM - IT	20	×1	×1
		Cortisone acetate	80-118	O	25	×0.8	×0.8
	Intermediate (12-36)	***Prednisone***	60	O	5	×4	×0.3
		Prednisolone	115-200	O - R	5	×5	×0.3
		Methylprednisolone	180	O – IV – IM – IS – ST – R	4	×5	×0.25
		Triamcinolone	30	O – IV – IM – IA – IL – ST – Ivit	4	×5	0
		Deflazacort	120	O	6	×4	0
	Long-lasting (36-72)	***Betamethasone***	300	O – IV – IM – IA – ID – IL	0.6	×25-40	0
		Dexamethasone	200	O – IV – IM – IA – IL	0.75	×30	0
Mineralocorticoids	Short-lasting (8-12)	***Dexoxycorticosterone acetate***	70	IM	-	0	×20
	Intermediate (12-36)	***Fludrocortisone***	200	O	2	×10	×250

*only for oral or intravenous administration; **: relative to hydrocortisone

Fluorinated glucocorticoids are highlighted in yellow

IA intra-articular, *ID* intra-dermal, *IL* intra-lesional, *IM* intra-muscular, *IS* intra-synovial, *IT* intra-thecal, *IV* intra-venous, *Ivit* intra-vitreal, *O* oral. *R* rectal. *ST* soft tissues

Drugs that increase plasma cortisol levels

Type of treatment	Drug	Mechanism of action		
		Impaired elimination	Decreased cytochrome P450 activity	Inhibition of hepatic metabolism
Anti-infectious	Erythromycin	•		
	Itraconazole		•	
	Ritanovir		•	
	Troleandomycin	•		
Contraceptive	Oral contraceptives	•		
Immunosuppressive	Cyclosporine			•

- . In 1912, Harvey Cushing reported on a 23-year-old-woman with "pituitary basophilism" who suffered from severe muscle weakness, weight gain, back pain, irregular menstruations, a round and large face, hypertrichosis, and hyperpigmentation
- this "polyglobular syndrome" was finally coined "Cushing's syndrome" by Bishop and Close
- In 1951, Germuth Jr.et al. observed focal necrosis of skeletal muscle of rabbits receiving cortisone, "explaining muscular weakness which appeared during this treatment"

Definition and epidemiology of GIM

- Excessive use of corticosteroids is not without risk, with potential severe musculoskeletal complications:
- In Cushing syndrome, impairment of bone status is described in 64–100% of cases, with skeletal fractures reported in11–76% of patients
- Primary GIM is linked to excessive production of cortisol by the adrenal glands by adrenal tumors (primary cause) or due to tumors that secrete ACTH (secondary cause)

- The prevalence of GIM varies depending on the **patient population, corticosteroid dose, and duration** of therapy.
- For example, GIM is slightly more prevalent in ectopic than in adrenal Cushing's syndrome
- Moreover, amongst patients with Cushing's disease, GIM is significantly more prevalent in male than female patients
- Studies indicate that 42–83% of patients with Cushing's syndrome develop myopathy, but severe muscle weakness is noted in only 2.4–21% of such patients

- Some corticosteroids more frequently induce GIM: if the risk increases with ***daily doses exceeding 10 mg prednisone*** (or equivalent) for more than 3–4 weeks
- Risk of muscular weakness is higher with the ***fluorinated steroids*** (triamcinolone, betamethasone, dexa-methasone).
- With prednisone/prednisolone, GIM is most likely to develop with doses over 40 mg/day, even if it may also occur with prolonged administration of lower doses

Populations at higher risk for GIM

- chronic inflammatory diseases (e.g. rheumatoid arthritis , systemic lupus erythematosus, etc.)
- critically ill patients (particularly those in intensive care units),
- malnourished people
- elderly individuals (who have reduced muscle regenerative capacity)
- patients with cancer or diseases affecting the respiratory muscles
- patients with prior muscle disorder, physically inactive patients

Physiopathology

❖Although not all of the pathophysiological mechanisms underlying GIM are fully determined, two in particular stand out:

- reduced protein synthesis
- increased protein degradation .

❖Glucocorticoids inhibit the synthesis of muscle protein by reducing the activity of **transcription factors and kinases** involved in protein translation.

❖They decrease the activity of the phosphatidylinositol 3-kinase/protein kinaseB/mammalian target of rapamycin (PI3K/Akt/mTOR) pathway, which is essential for muscle growth and survival

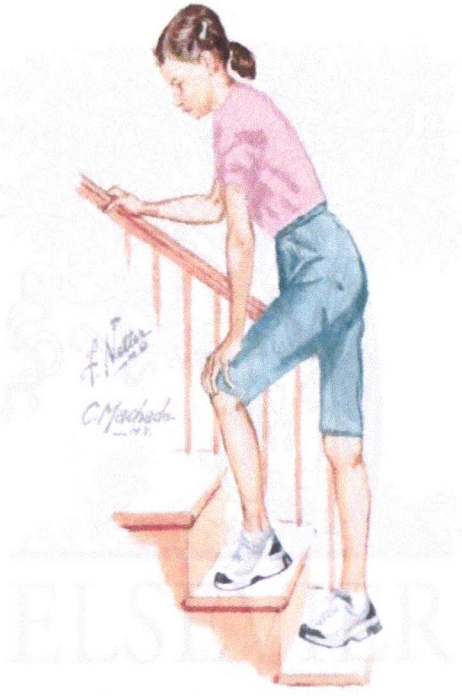
- Glucocorticoids reduce muscle contractile force by decreasing the expression of contractile proteins. such as myosin and actin.

- Glucocorticoids ultimately alter the structure of muscle fibres, leading to a reduction in fibre size and loss of muscle strength.
- Glucocorticoids primarily affect **type II (fast-twitch) muscle fibres,** which are more susceptible to glucocorticoid-induced atrophy than type I (slow-twitch) fibres

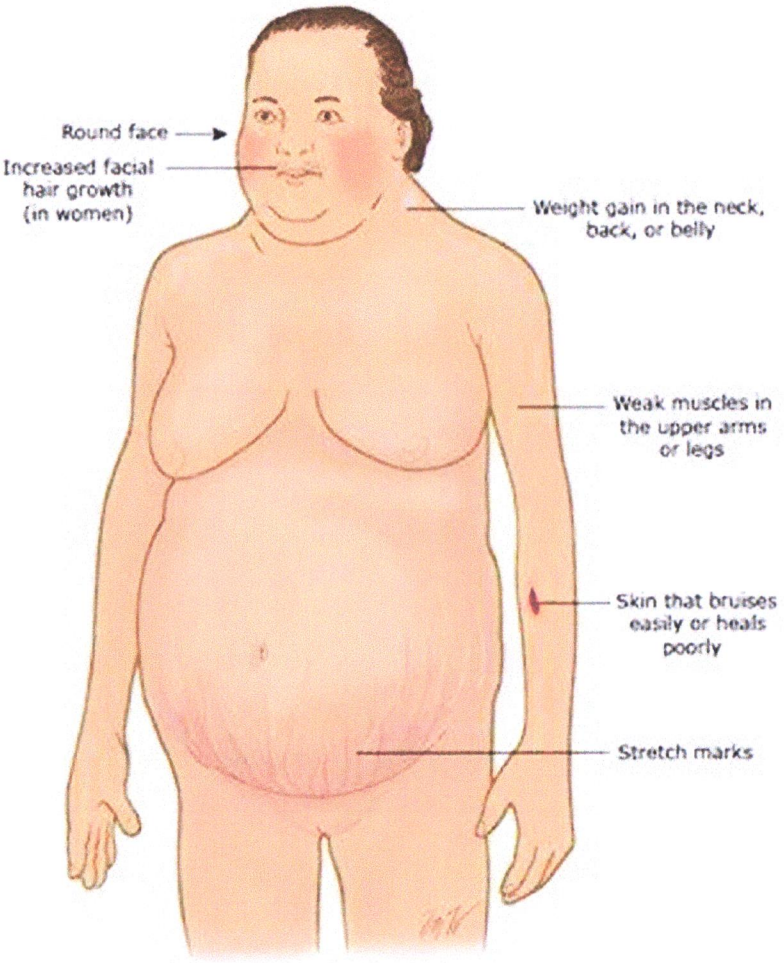
Clinical features

- The chronic form (the most frequent one)typically presents insidiously, with slow progression, and is marked by painless, symmetric proximal muscle weakness
- Significant long-term muscle wasting, more prominently and earlier in the lower limbs(quadriceps, hip flexors) than in the upper limbs (shoulders).

- Patients usually first experience **difficulty climbing stairs** or **rising from a seated position**, followed by **trouble lifting objects** overhead; however, in some cases, **upper-limb girdle weakness** may be more pronounced, some may also report **generalised myalgia**
- Usually, the muscles of feet, hands, face, and sphincter are spared , but respiratory muscles may b involved



- **Fat redistribution** (accumulation of fat incertain adipose tissue depots, particularly in the face [“moonface”], the nape of the neck [“buffalo hump”], and visceral compartments)

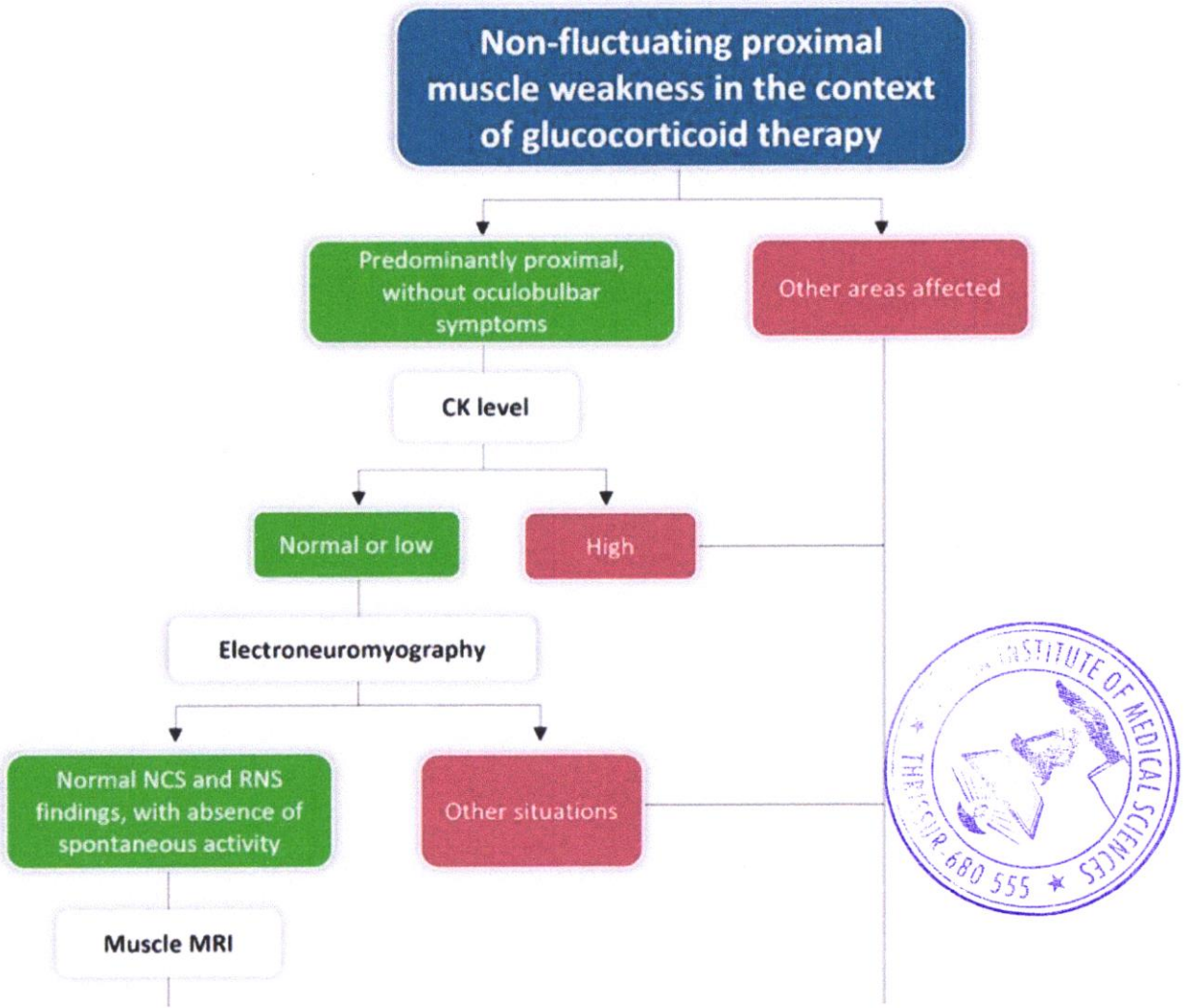


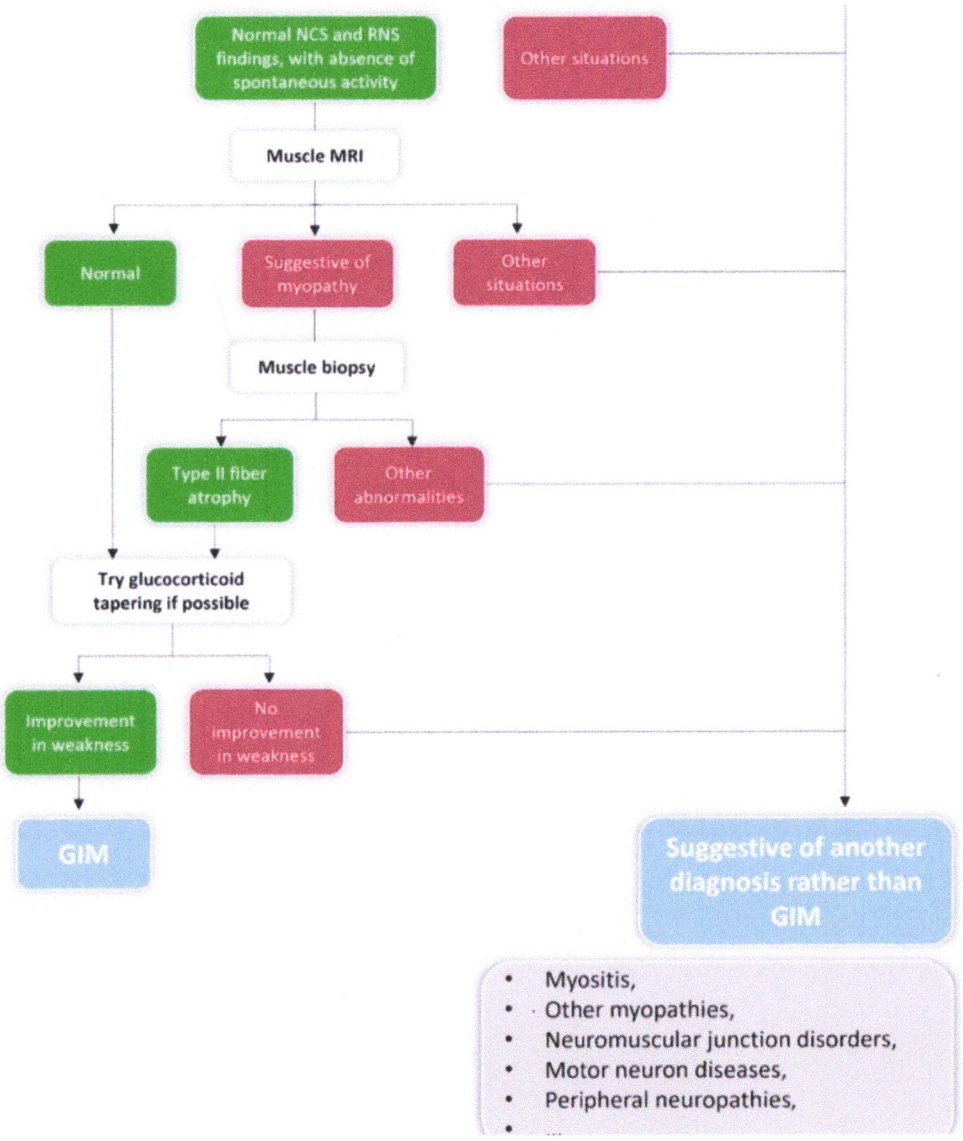
- Very rarely, GIM may present acutely, usually within1–4 weeks of treatment initiation and most often in critically ill patients requiring ventilatory support
- Acute GIM has also been reported following epidural or intra-articular steroid injections, and even with inhaled glucocorticoids

Laboratory and imaging studies

- Elevated serum levels of creatine kinase (CK), aldolase, aspartate aminotransferase(AST), or lactate dehydrogenase (LDH)
- However, in chronic GIM, levels of muscle enzymes (particularly CK)are typically normal or only mildly elevated

- In contrast, the acute form of GIM (often associated with rhabdomyolysis) is usually marked by markedly elevated serum CK levels, and in some cases, myoglobinuria


Non-fluctuating proximal muscle weakness in the context of glucocorticoid therapy
Predominantly proximal, without oculobulbar symptoms
Other areas affected
CK level
Normal or low
High
Electroneuromyography
Normal NCS and RNS findings, with absence of spontaneous activity
Other situations
Muscle MRI


Normal NCS and RNS findings, with absence of spontaneous activity
Other situations
Muscle MRI
Normal
Suggestive of myopathy
Other situations
Muscle biopsy
Type II fiber atrophy
Other abnormalities
Try glucocorticoid tapering if possible
Improvement in weakness
No improvement in weakness
GIM
Suggestive of another diagnosis rather than GIM
Myositis,
Other myopathies,
Neuromuscular junction disorders,
Motor neuron diseases,
Peripheral neuropathies,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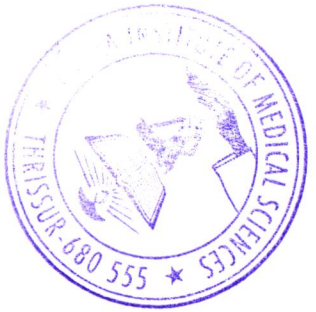
Electrophysiological studies

In patients with suspected myopathy, routine nerve conduction studies should always be performed, particularly to exclude other motor disorders (e.g. motor neuron disease or neuromuscular junction disorders). In severe cases of myopathy, motor nerve conduction studies may reveal reduced compound muscle action potential (CMAP) amplitudes, whilst latencies and conduction velocities remain normal. However, nerve conduction studies are generally normal unless there is a coexisting sensory or sensorimotor neuropathy. In GIM, electromyography (EMG) is typically normal unless the myopathy is pronounced; in such cases, EMG may show a mild reduction in CMAP and the presence of low-amplitude, short-duration motor unit potentials without evidence of active denervation [57].



Radiological studies

Magnetic resonance imaging (MRI) enables assessment of whole-body muscle size and fat infiltration. Although fatty infiltration and truncal muscle atrophy have been reported in GIM, [58] no study has specifically evaluated the utility of MRI for diagnosis or management of the condition [59]. Muscle echo intensity has been observed to track GIM progression over time and may indicate early response to therapy [60]. More recently, muscle ultrasound has been used to monitor structural muscle changes in GIM [61].

Histopathological studies

Muscle biopsy is an important diagnostic procedure in neuromuscular practice, [62] but it is not required for the diagnosis of GIM. Nevertheless, histopathological changes in muscle tissue have been extensively analysed since the 1950 s to better understand the pathological and phenotypic changes induced by exogenous and endogenous glucocorticoid excess [12, 55, 63–66]. If a muscle biopsy is performed, it typically reveals muscle fibre atrophy, preferentially affecting type II fibres (particularly type IIb, which are high in myofibrillar ATPase) whilst sparing type I fibres (low in ATPase and rich in succinate dehydrogenase) (Fig. 2). However, type II fibre atrophy is non-specific and may also be observed in other conditions, such as disuse or chronic alcohol consumption. Nerve biopsy shows no evidence of inflammation [67].

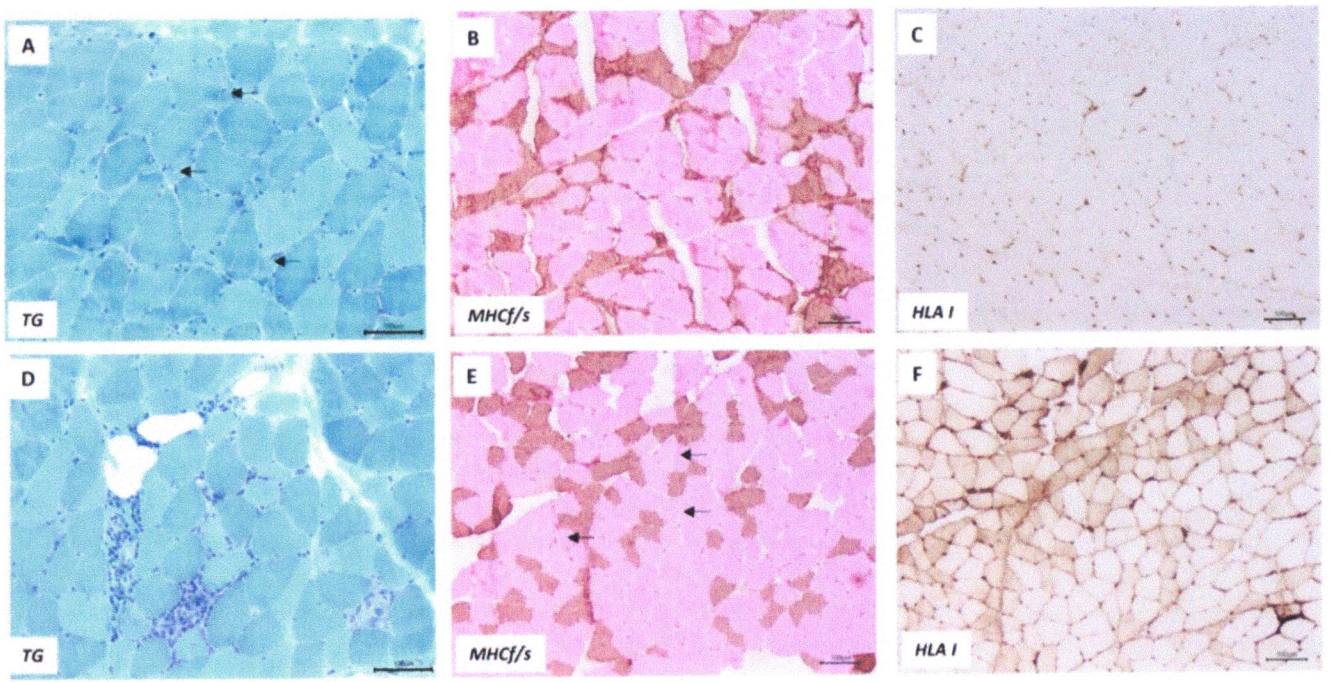


Fig. 2 Histopathological aspects observed in cortisone-induced myopathy compared to inflammatory myopathy. **A–C** Corticosteroid-induced myopathy. Panel **A** shows selective atrophy of muscle fibres (black arrow), predominantly affecting type II fibres (modified Gomori trichrome), as demonstrated in panel **B** by MHC-fast/slow immunostaining. Type II fibres appear brown, in contrast to type I fibres, which stain pink and display normal size. HLA class I immunostaining reveals an absence of sarcolemmal expression on muscle fibres, with normal capillary staining as demonstrated in panel **C**. **D–F**: Overlap myositis. Panels **D** and **E** show endomysial and perimysial inflammatory infiltrates with fibres being surrounded by inflammatory cells. Atrophy involves both type II and type I fibres (black arrow in **E**). HLA class I immunostaining demonstrates diffuse sarcolemmal expression in all muscle fibres (panel **F**)

Management and therapeutic strategies

1. Glucocorticoid dose adjustment :

- The primary strategy for managing GIM is the reduction or discontinuation of glucocorticoids as the condition is directly linked to the dose and duration of exposure.
- Tapering or withdrawing glucocorticoids can result in significant improvements in muscle strength within 3–4 weeks
- Switch from from fluorinated to non-fluorinated compounds like prednisone and hydrocortisone
- Alternate-day dosing regimens

2. Physical therapy and rehabilitation

- Moderate endurance and resistance training can attenuate glucocorticoid-induced muscle atrophy and weakness
- Resistance training (effective for counteracting muscle atrophy)
- Aerobic exercise (which helps improve mitochondrial function)

3. Promising pharmacological approaches

- GH and IGF-1- GHs stimulate the production of IGF-1, which plays a crucial role in muscle protein synthesis and myogenesis. They ameliorate glucocorticoid-induced muscle atrophy

- Branched-chain amino acids (BCAAs) show protective effects against glucocorticoid-induced muscle atrophy.
- Creatine supplementation

- Androgens, such as testosterone and dehydroepiandrosterone (DHEA), have been investigated for their potential to counteract the catabolic effects of glucocorticoids.
- Myostatin inhibitor, glutamine is an amino acid that plays a crucial role in muscle protein synthesis and repair.

Conclusion

- GIM remains a significant and often overlooked complication of long-term corticosteroid therapy.
- Early recognition, optimised corticosteroid regimens, and structured rehabilitation programmes are crucial for mitigating muscle loss and preserving function.

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