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Glucocorticoid-induced myopathy in people with asthma: a systematic review

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ABSTRACT

Objectives: To review the current literature on the evidence and the underlying characteristics of glucocorticoids (type, dosage, and duration) associated with myopathy in asthma.

Data Sources: Four electronic databases were searched to October 19, 2020.

Study Selection: Inclusion criteria: adults or adolescents with asthma, taking systemic glucocorticoids, and measures of muscle impairments.

Results: Nine studies met the eligibility criteria. The methodologic quality of most studies was fair or good. Two studies reported significantly lower inspiratory muscle function in outpatients taking daily oral glucocorticoids (≥ 10 mg), but one study reported no such difference. No differences were found in limb muscle strength in one study. Only 11–36% patients with acute exacerbation taking glucocorticoids intravenously suffered from limb muscle weakness during/after critical care admissions. Two studies reported significant associations between *dosage* of oral glucocorticoid use and inspiratory and limb muscle function, whereas seven studies did not find any significant correlations among the characteristics of systemic glucocorticoids and myopathy. Two studies comparing people with non-glucocorticoid dependent asthma taking inhaled glucocorticoid and healthy people did not find any significant differences in their inspiratory muscle strength and endurance.

Conclusions: There were limited studies and inconsistent results on glucocorticoid-induced myopathy in people with asthma, and its association with the characteristics of glucocorticoids use. We recommended future studies should use a commonly accepted operational definition of myopathy, utilize a cohort study design, measure the cumulative dosage of glucocorticoids, and integrate possible confounding factors in the analysis.

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Corticosteroid; musculoskeletal; muscle atrophy; muscle weakness; steroid

Introduction

Glucocorticoids are commonly used for people with asthma to reduce airway inflammation. Inhaled glucocorticoids, designed to more effectively reduce airway inflammation locally, are used extensively as a maintenance therapy for people with asthma (1). Systemic glucocorticoids, in the form of oral or intravenous (IV), may be added to treatments during acute exacerbation of asthma, or on a day-to-day basis for people with moderate to severe asthma (1,2). Systemic glucocorticoid use has been associated with a wide range of potential adverse effects, such as opportunistic infection, osteoporosis, muscular and gastrointestinal complications, and diabetes (3).

Myopathy has been described as an adverse effect of glucocorticoids. There is scientific evidence on the pathophysiological basis of glucocorticoid-induced myopathy (summarized in Figure 1). Although there is no single definition of myopathy, the clinical features of myopathy may include muscle wasting, weakness, and/or fatigability (15), affecting the respiratory and/or limb muscles (16). In the limbs, glucocorticoids usually affect the proximal muscles symmetrically; and may involve both upper and lower extremities, although the legs tend to be affected to a greater extent (15). Histologically, glucocorticoid-induced myopathy is characterized by a decrease in the size of fast-twitch or type II muscle fibers (particularly IIX and IIB) (17), loss of myosin filaments

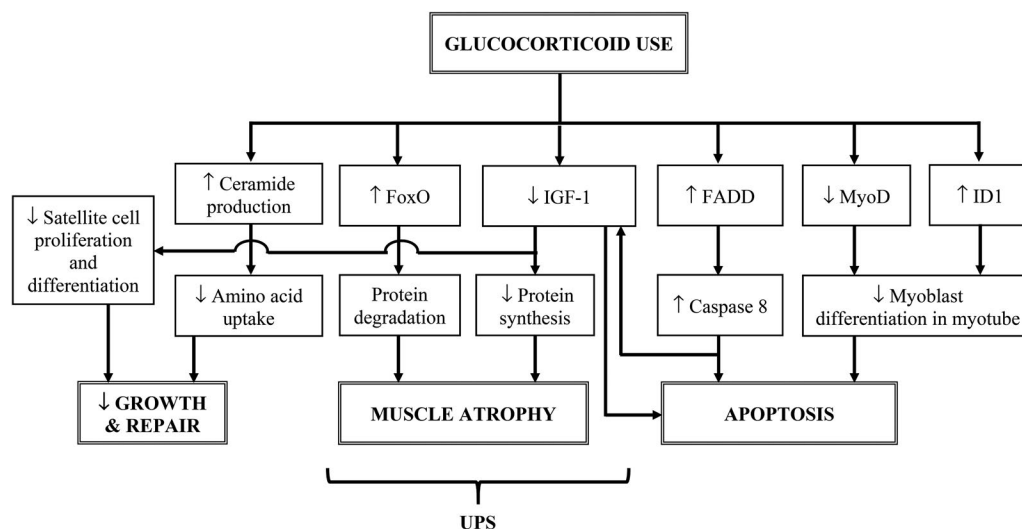


Figure 1. Pathophysiological mechanism of glucocorticoid-induced myopathy. Glucocorticoid-induced myopathy alters several protein expressions involved in the ubiquitin-proteasome system (UPS). Specifically, through an overexpression of forkhead box (FoxO) transcription factors, glucocorticoids lead to myofibrillar protein degradation, resulting in significant muscle fiber atrophy (4,5). Glucocorticoids also cause reduced content of myoblast determination protein 1 (MyoD), and an increased content of inhibitors of DNA-binding 1 (ID1), which lead to an inhibition of myoblast differentiation into myotubes to potentiate myoblast proliferation (6). In addition, glucocorticoids inhibit insulin-like growth factor 1 (IGF-1) signaling, which leads to suppression of the anabolic effect of protein synthesis in skeletal muscle, and reduction of satellite cell proliferation and differentiation for growth and repair (7). IGF-1 inhibition also causes catabolic processes in the muscle cells leading to an activation of the UPS and apoptosis, resulting in muscle atrophy (7,8). Moreover, glucocorticoids increase the production of ceramide in skeletal muscle (9–11), which leads to an attenuation of growth and repair via an inhibition of amino acid uptake, suppression of IGF-1 induced protein synthesis and differentiation, and the induction of cell cycle arrest. This stimulates myofibrillar protein degradation via the UPS, oxidative stress and mitochondrial dysfunction resulting in muscle atrophy (12,13). Furthermore, the activation of Fas-associated protein with death domain (FADD) also results in glucocorticoid-induced apoptosis in muscle cells (10,11,14). These processes together result in muscle fiber atrophy, decreased growth and repair in skeletal muscles.

in sarcomeres with preservation of actin filaments and z-bands, and necrosis (18,19). Myopathy is more commonly associated with the use of fluorinated glucocorticoids, i.e. dexamethasone, but can also be associated with non-fluorinated glucocorticoids, i.e. beclomethasone, methylprednisolone, prednisone, prednisolone and hydrocortisone (20). People with glucocorticoid-induced myopathy suffer considerable morbidity as a result of their muscle weakness. For example, people with chronic lung diseases with inspiratory muscle weakness from glucocorticoids may experience increased dyspnea, decreased exercise tolerance, and reduced quality of life (21). Critically ill patients with limb muscle weakness may need intensive physical rehabilitation (19,22).

Based on the current literature it is unclear which type (fluorinated vs. non-fluorinated) dosage, and duration of glucocorticoid may be associated with myopathy in people with asthma. A better understanding of the specific type of glucocorticoid, the minimum daily dosage and duration of glucocorticoid therapy that are associated with myopathy in people with asthma, will help identify those at high risk of glucocorticoid-induced myopathy and will guide the assessment and treatment of muscle impairments. The objectives of this systematic review are:

1. To summarize the methods used to detect myopathy in the literature on glucocorticoid-induced myopathy in people with asthma; and
2. To review the evidence of glucocorticoid-induced myopathy in people with asthma, and the underlying characteristics of glucocorticoids (type, dosage and duration) associated with myopathy.

Methods

A systematic review was performed based on PRISMA guidelines (23) (PROSPERO registration number CRD42020142448). The search strategy was constructed using the following databases: MEDLINE, EMBASE, CINAHL Plus and Cochrane CENTRAL databases; and included studies from inception to October 19, 2020. Studies were included if they comprised (1) adults or adolescents with asthma; (2) receiving treatment of systemic glucocorticoids (oral and/or IV); and (3) measures of myopathy (including any impairments of muscle structure or function). Studies were excluded if they were (1) published in a language other than English; (2) included human subjects with neuromuscular disorders or rheumatological conditions; or (3) reviews, meta-analyses, editorials,

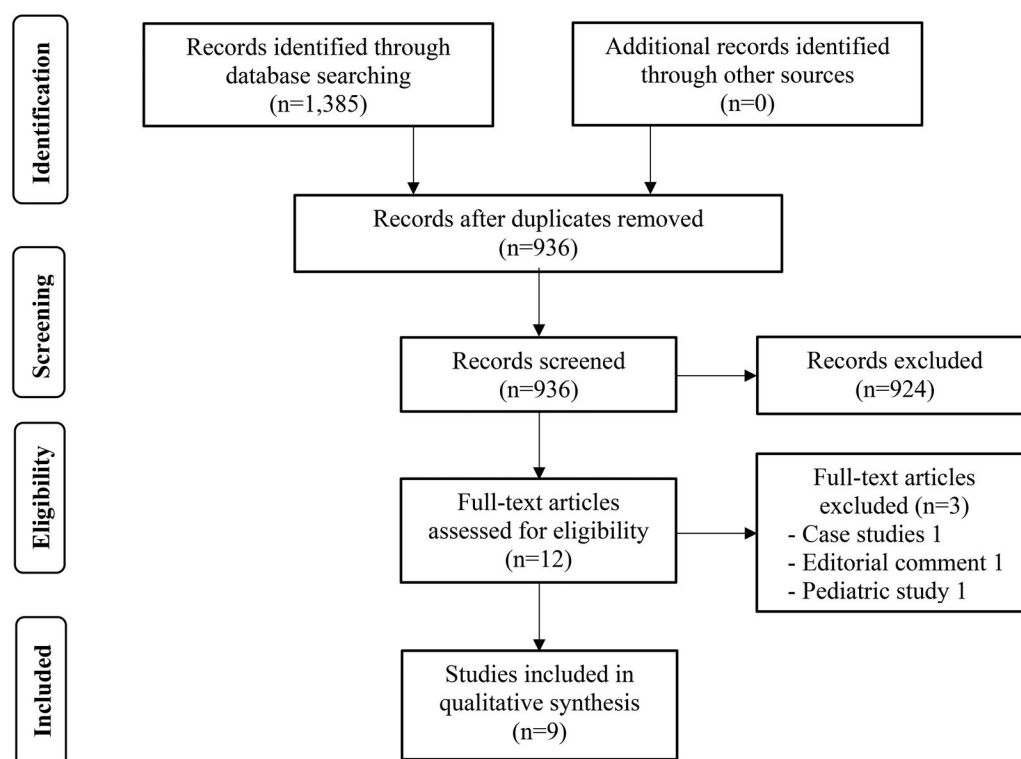


Figure 2. PRISMA flow diagram showing study selection.

conference abstracts, guidelines, commentary, case studies, or case reports.

Terms that were used in the searches included: (1) characteristics of respiratory or limb muscles, including anatomical and cellular levels, muscle size, and contractile functions, and abnormalities; (2) steroids, corticosteroids, or different type of glucocorticoids; and (3) aspergillosis or asthma (listed in Table 1S in Supplementary Materials). Two authors (KW and AM) independently reviewed the titles and abstracts of the retrieved articles to determine if the studies met the eligibility criteria.

The dosages of glucocorticoids extracted from the articles were converted based on anti-inflammatory potency by author (KW) to the most commonly used glucocorticoids in asthma, such as budesonide for inhaled glucocorticoids, prednisone for oral glucocorticoids, and methylprednisolone for glucocorticoids administered through IV (32,33). Due to the large variability of daily dosage and duration of the glucocorticoids use, we were unable to conduct any meta-analysis.

Quality assessment

A methodologic quality assessment of the articles was performed by two reviewers (KW and AM), independently, using the National Heart, Lung, and Blood Institute (NIH) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (34). Reviewers

answered 14 questions for each study; and provided an overall study quality rating as good, fair, or poor (Table 1). No studies were excluded based on study quality.

Results

Nine studies met the eligibility criteria for this systematic review (Figure 2)—five cross-sectional studies (24–28), three retrospective cohort studies (16,30,31), and one prospective cohort study (29). The study design, demographic and spirometry data are summarized in Table 2. Six studies focused on adults with glucocorticoid-dependent asthma (16,24–28); three studies were in the setting of an *acute asthma exacerbation* requiring critical care admission and mechanical ventilation (29–31). A total of 244 adults with glucocorticoid-dependent asthma, and 205 adults and adolescents with acute asthma exacerbation, were included across the nine studies. These studies also included 64 adults with non-glucocorticoid-dependent asthma (as asthma controls). The mean $\pm$ SD age of adults with glucocorticoid-dependent asthma from five studies was 52.6 ± 13.0 years (24–28). One study with glucocorticoid-dependent asthma listed only the number of subjects in various age groups (52% of the subjects were >40 years of age), hence it was not included in the age calculation (16). The mean $\pm$ SD age of adults and adolescents with acute asthma

Table 1. Quality assessment of the nine studies.

Study focus	Glucocorticoid-dependent asthma					Acute asthma exacerbation			
	Bowyer (1985) (16)	Picado (1990) (24)	Mak (1993) (25)	Perez (1996) (26)	Akkoca (1999) (27)	Pereira (2015) (28)	Douglass (1992) (29)	Leatherman (1996) (30)	Behbehani (1999) (31)
First author (year)									
1. Research question/objective: clearly stated?	Y	Y	Y	Y	Y	Y	Y	Y	Y
2. Study population: clearly specified and defined?	Y	Y	N	Y	Y	Y	Y	Y	Y
3. At least 50% participation rate of eligible persons?	C	C	C	C	C	C	C	C	Y
4. Groups recruited from the same or similar populations (including the same time period)? Inclusion and exclusion criteria pre-specified and applied uniformly to all participants?	Y	Y	C	Y	C	Y	Y	C	Y
5. Sample size justification, power description, or variance and effect estimates provided?	N	N	N	N	N	Y	N	N	N
6. Exposure(s) of interest measured prior to the outcome(s) being measured?	Y	Y	Y	Y	Y	Y	Y	Y	C
7. Sufficient timeframe to see an association between exposure and outcome if it existed?	C	Y	Y	Y	Y	Y	C	Y	C
8. Examining different levels of the exposure as related to the outcome?	Y	Y	Y	Y	Y	Y	Y	Y	N
9. Exposure measure and assessment: clearly defined, valid, reliable, and implemented consistently across all study participants?	N	Y	Y	Y	Y	Y	Y	Y	Y
10. The exposure(s) assessed more than once over time?	Y	N	C	N	N	N	C	Y	C
11. Outcome measures: clearly defined, valid, reliable, and implemented consistently across all study participants?	Y	Y	Y	Y	Y	Y	Y	Y	Y
12. Outcome assessors blinded to the exposure status of participants?	C	Y	C	C	C	C	C	C	C
13. Loss to follow-up after baseline 20% or less?	A	A	A	A	A	A	A	A	A
14. Key potential confounding variables measured and adjusted statistically for their impact or the relationship between exposure(s) and outcome(s)?	N	N	N	Y	Y	N	N	N	N
Quality rating	FAIR	FAIR	FAIR	GOOD	GOOD	FAIR	POOR	GOOD	POOR

Note: A: not applicable; C: cannot determine; N: no; Y: yes.

exacerbation was 45.2 ± 14.8 years (29,31). One study with people with acute asthma exacerbation reported the median (min-max) age of their sample as 34 (16–78) years, and thus was not included in the age calculation (30). Males comprised 39% of all adults with glucocorticoid-dependent asthma (16,24–28), and 50% of all adults and adolescents with acute asthma exacerbation in three studies (29–31). The median (min-max) length of hospitalization in one study with patients with acute asthma exacerbation was 7 (2–49) days (31). The mean $\pm$ SD duration of mechanical ventilation in another study with people with acute asthma exacerbation was 6.6 ± 6.6 days (29).

For the glucocorticoid-dependent asthma group, four of these studies had patients on their minimum

maintenance dose of oral glucocorticoids (24–27); two studies specified an average daily dose of ≥ 10 mg of prednisone (26,27); three studies had patients taking oral glucocorticoids for at least one year (25–27); and one study did not specify any characteristics of the glucocorticoids use (28). Some people with glucocorticoid-dependent asthma were also on high dose of inhaled glucocorticoids (i.e. an average daily dose of $\geq 1,200$ μ g of budesonide or equivalent) (25,28), short-acting beta-agonist, ipratropium bromide, oral theophylline (25). and/or long-acting beta-agonist (28). Three studies did not provide information on the other asthma medications taken by their subjects (24,26,27).

Different inclusion criteria were used for the *non-glucocorticoid-dependent asthma group* (summarized

Table 2. Study design, demographic and spirometry data in the nine studies.

First authors (year)	Study groups (n)	Description of asthma control group	Study design	Age (mean $\pm$ SD years)	Sex (M:F)	FEV ₁ (mean $\pm$ SD% pred.)
Bowyer (1985) (16)	1. GC-dependent asthma on systemic GC: • ≥ 40 mg (n=18) or • none to < 40 mg (n=42) 2. Healthy control (n=71)	–	Retrospective cohort study	< 30 y (n=20), 30–40 y (n=9), > 40 y (n=31) < 30 y (n=21), 30–40 y (n=24), > 40 y (n=26)	3. 23:37 4. 31:40	NR
Picado (1990) (24)	5. GC-dependent asthma on systemic GC (n=34) 6. Non-GC-dependent asthma control (n=34)	Age- and sex-matched with GC-dependent asthma group	Cross-sectional study	55.9 $\pm$ 10.6 55.9 $\pm$ 10.7	7. 11:23 8. 11:23	54 $\pm$ 16 73 $\pm$ 22
Mak (1993) (25)	9. GC-dependent asthma on systemic GC (matched) (n=12) 10. Non-GC-dependent asthma control (n=12) 11. GC-dependent asthma on systemic GC (unmatched)* (n=18)	–	Cross-sectional study	59.5 $\pm$ 10.4 61.4 $\pm$ 9.3 57.1 $\pm$ 14.9	12. 6:6 13. 6:6 14. 8:10	NR
Perez (1996) (26)	15. GC-dependent asthma on systemic GC (n=19) 16. Non-GC-dependent asthma control (n=16)	Receiving occasional short courses (< 2 weeks) of oral GC for exacerbation	Cross-sectional study	52.7 $\pm$ 9.0 45.5 $\pm$ 3.6	17. 13:6 18. 10:6	50 $\pm$ 3 55 $\pm$ 4
Akkoca (1999) (27)	19. GC-dependent asthma on systemic GC (n=12) 20. Non-GC-dependent asthma control (n=14)	Moderate to severe asthma, taking an average daily dose of > 800 μ g of inh. budesonide or equivalent for ≥ 1 year	Cross-sectional study	45.7 $\pm$ 15.8 43.9 $\pm$ 8.4	21. 2:10 22. 4:10	67 $\pm$ 22 71 $\pm$ 21
Pereira (2015) (28)	GC-dependent asthma on systemic GC (n=25)	–	Cross-sectional study	49.8 $\pm$ 12.6	7:18	59 $\pm$ 22
Douglass (1992) (29)	Acute asthma exacerbation requiring critical care admission and mechanical ventilation receiving GC (n=25)	–	Prospective cohort study	39 $\pm$ 17	5:20	NR
Leatherman (1996) (30)	Acute asthma exacerbation requiring critical care admission and mechanical ventilation receiving GC (107 episodes; n=94)	–	Retrospective cohort study	34 (16–78) [†]	50:44	NR
Behbehani (1999) (31)	Acute asthma exacerbation requiring critical care admission and mechanical ventilation receiving GC (n=86)	–	Retrospective cohort study	47 $\pm$ 16	48:38	NR

Note. All asthma control groups were not on regular systemic glucocorticoids. *This glucocorticoid-dependent asthma on systemic glucocorticoids group were not able to match for their demographic and indices of airflow limitation and hyperinflation to a stable chronic airflow limitation group in the study; [†]: median (min-max); NR: not reported; F: female; FEV₁: forced expiratory volume in one second; GC: glucocorticoids; inh: inhaled; M: male; y=years.

in Table 2). The exclusion criteria for each of these nine studies are shown in Table 3. The three studies on patients with acute asthma exacerbation did not have any exclusion criteria (29–31); however two of these studies specifically described the potential confounding factors, e.g. sepsis, renal or hepatic failure, alcoholic abuse, or smoking history (29,31).

Quality assessment

The quality ratings of the studies are shown in Table 1. Three studies were rated as good (26,27,30), four as fair (16,24,25,28), and two as poor (29,31). All studies clearly stated their research questions, objectives, and described the validity and reliability of their outcome measures. Most studies provided well defined exposures, implemented the exposures prior to measurement of outcomes, and explored different levels of exposures. However, most studies were unclear on the participation rate, and whether the outcome assessors were blinded to the exposure status of their subjects. Furthermore, most studies did not provide information on the sample size justification, power description, variance and effect estimates. None of the studies adjusted for covariates in their analysis.

Methods to detect myopathy

Various methods had been used to detect myopathy, including respiratory and limb muscle strength and endurance, nerve conduction studies and needle electromyography (EMG), muscle biopsy, urine and serum markers assessing muscle damage, and broader definitions of limb muscle strength (i.e. the degree of clinically significant muscle weakness), in the intensive care unit setting. These methods are summarized in Table 4.

Characteristics of glucocorticoid use

The characteristics of glucocorticoid use, including type, dosage, methods to calculate the average daily doses, delivery mode, and duration of glucocorticoids, are summarized in Table 5. Among the six studies of people with glucocorticoid-dependent asthma, five studies used non-fluorinated glucocorticoids orally (16,24–26,28); one did not specify the type of glucocorticoids they used (27). In studies of people with acute asthma exacerbation, one study included both fluorinated and non-fluorinated glucocorticoids intravenously (29); and two included people using only IV non-fluorinated glucocorticoids (30,31).

Five studies included patients taking the systemic glucocorticoids for at least one year (24–28); four studies

did not specify the duration (16,29–31). The mean dose of oral glucocorticoids used in five studies with people with glucocorticoid-dependent asthma was an average daily dose of ≥ 10 mg of prednisone or equivalent (16,24,26–28); one study had people with glucocorticoid-dependent asthma using 8 mg average daily dose of prednisone or equivalent (25). Massive dosages of systemic glucocorticoids to treat asthma (≥ 160 mg average daily dose of Methylprednisolone or equivalent, which is equivalent to 200 mg average daily dose of prednisone or equivalent) were used in patients with acute asthma exacerbation (29–31). Only five studies reported the methods they used to calculate the average daily dose: two studies used the daily dose over two to six months prior to the commencement of the studies (16,26); one used the typical dose used in the hospital (30); another used the initial dose of systemic glucocorticoids (31).

Five studies described of patients with glucocorticoid-dependent asthma used inhaled glucocorticoid (24–26,28,29). Two of these studies described the average daily dose of inhaled glucocorticoid that the patients were using, with an average daily dose of $>1,200 \mu\text{g}$ (25) and $>1,600 \mu\text{g}$ of budesonide or equivalent (28). Only two studies included an asthma control group with patients with non-glucocorticoid-dependent asthma (26,27), and only one study described the average daily dose and duration of inhaled glucocorticoid use ($>800 \mu\text{g}$ of budesonide or equivalent for ≥ 1 year) (27).

The adverse effects of glucocorticoids on muscles in people with asthma

The results from studies on clinically stable asthma are summarized in Table 6. Additional details of the results from these studies are also described below.

One study found lower inspiratory muscle *strength*, measured by maximal inspiratory pressure, in people with glucocorticoid-dependent asthma taking oral glucocorticoid when compared to those with non-glucocorticoid-dependent asthma (44.2 ± 13.0 vs. 59.4 ± 18.5 cm H₂O, $p < .01$) (27), but two studies reported no such difference between the two groups (24,26). One study found lower inspiratory muscle *endurance* in people with glucocorticoid-dependent asthma taking oral glucocorticoid compared to those with non-glucocorticoid-dependent asthma ($43 \pm 3\%$ predicted vs. $65 \pm 4\%$ predicted, $p < .0001$) (26); another study did not find any significant differences between the two groups (24). Two studies found no significant differences in maximal *expiratory* pressure between people with glucocorticoid-dependent asthma taking oral glucocorticoids and those with

Table 3. Exclusion criteria used in the nine studies.

Study focus	Glucocorticoid-dependent asthma					Acute asthma exacerbation			
	Bowyer (1985) (16)	Picado (1990) (24)	Mak (1993) (25)	Perez (1996) (26)	Akkoca (1999) (27)	Pereira (2015) (28)	Douglass (1992) (29)	Leatherman (1996) (30)	Behbehani (1999) (31)
First author (year)									
Significant hypoxemia									
Malnutrition									
Coexisting respiratory disease									
Coexisting neuromuscular disease									
Coexisting endocrine disease									
Coexisting heart disease									
Coexisting metabolic disease									
Coexisting neuropathic disorder									
Coexisting joint disorders									
Coexisting musculoskeletal disorder									
Smoking—current									
Smoking—former									
History of exacerbation requiring emergency admission									
Use of antibiotics									
History of alcoholic abuse									

Note. • indicates the study included the respective items as exclusion criteria.

Table 4. Methods used to detect myopathy in the nine studies.

Study focus	Glucocorticoid-dependent asthma					Acute asthma exacerbation			
	Bowyer (1985) (16)	Picado (1990) (24)	Mak (1993) (25)	Perez (1996) (26)	Akkoca (1999) (27)	Pereira (2015) (28)	Douglass (1992) (29)	Leatherman (1996) (30)	Behbehani (1999) (31)
First author (year)									
Inspiratory muscle strength	•	•	•	•	•	•			
Expiratory muscle strength	•	•	•		•				
Inspiratory muscle endurance/fatigability		•	•	•					
Limb muscle strength	•	•	•						
Clinically significant muscle weakness [‡]							•	•	•
Nerve conduction study							•	•	•
Electromyography							•	•	•
Muscle biopsy		•					•	•	
Serum creatine kinase	•								
Other serum and urine markers of muscle damage [§]	•								
Urine marker of muscle damage	•								

Note. • indicates the study included the respective outcome measure; [†]Clinically significant muscle weakness included inability to perform ADL independently, the need for inpatient physical rehabilitation, and/or a strength rating of less than 4 on a 0–5 scale in one or more major muscle groups; [§]Other serum markers of muscle damage included aldolase, lactate dehydrogenase, potassium, and serum glutamic oxaloacetic transaminase.

Table 5. Information on the glucocorticoids used by people with asthma in the nine studies.

First Authors (Year)	Study Groups	Glucocorticoids [Oral GC (Inhaled GC)]	Dosages [‡] , Delivery Modes	Methods to Calculate the Average Daily Doses	Durations (years)
Bowyer (1985) (16)	GC-dependent asthma	Prednisone	≥40 mg, oral 0 to <40 mg, oral	Previous 2–3 months	NR
Picado (1990) (24)	GC-dependent asthma	Prednisone (Beclomethasone)	11.9 ± 3.7 mg, oral (dosage of inh. GC: ^{NR})	NR	7.9 ± 3.7
Mak (1993) (25)	1. GC-dependent asthma (matched) 2. GC-dependent asthma (unmatched) [†]	1. Prednisolone (Beclomethasone) 2. Prednisolone	8.0 ± 2.8 mg, oral (>1,200 µg [‡] , inh.) 8.0 ± 3.1 mg, oral	NR	1. 16.8 ± 9.1 2. 13.3 ± 9.5
Perez (1996) (26)	1. GC-dependent asthma 2. Non-GC-dependent asthma control	1. Prednisone (95% subjects used inh. GC; type of GC use: ^{NR}) 2. 94% subjects used inh. GC; type of GC use: ^{NR})	1. 20.7 ± 2.4 mg, oral (dosage of inh. GC use: ^{NR})	1. Previous 6 months 2. NR	1. 5.0 ± 1.4 2. 1
Akkoca (1999) (27)	1. GC-dependent asthma 2. Non-GC-dependent asthma control	1. NR 2. Beclomethasone	1. 10–20 mg, oral 2. >800 µg [‡] , inh.	NR	1. 9.8 ± 9.9 2. ≥1
Pereira (2015) (28)	GC-dependent asthma	Prednisone and/or (Budesonide)	≥10 mg, oral and/or (>1600 µg inh.)	NR	≥1
Douglass (1992) (29)	Acute asthma exacerbation requiring critical care admission and mechanical ventilation	Dexamethasone or Hydrocortisone (44% of subjects used some inh. GC; type of GC use: ^{NR})	160 mg [§] , IV or 200 mg [§] , IV (dosage of inh. GC use: ^{NR})	NR	NR
Leatherman (1996) (30)	Acute asthma exacerbation requiring critical care admission and mechanical ventilation	Methylprednisolone	500 mg [§] , IV	Typical dosage	NR
Behbehani (1999) (31)	Acute asthma exacerbation requiring critical care admission and mechanical ventilation	Methylprednisolone or Hydrocortisone	260 ± 154 mg [§] , IV	Initial dosage	NR

Note. Most patients on systemic glucocorticoids were also on some inhaled glucocorticoids.

^{NR}: not reported; [‡]All numbers were in average daily dose of prednisone unless specified otherwise; [†]This glucocorticoid-dependent asthma group was not able to match for their demographic and indices of airflow limitation and hyperinflation to stable chronic airflow limitation group; [‡]The volume was in average daily dose of budesonide or equivalent; [§]The volume was in average daily dose of methylprednisone; GC: Glucocorticoid; inh.: inhaled; IV: intravenous.

non-glucocorticoid-dependent asthma (24,27). Only one study explored the limb muscle strength and found no significant difference in deltoid muscle strength between the two groups (24).

Two studies comparing people with non-glucocorticoid dependent asthma taking inhaled glucocorticoid and healthy people did not find any significant differences in their inspiratory muscle strength (26,27) and inspiratory muscle endurance (26).

In studies focused on patients with acute asthma exacerbation requiring critical care admission for mechanical ventilation receiving systemic glucocorticoids, some patients (ranged from 35% to 88%) were concurrently treated with neuromuscular blocking agents. All three studies reported some degree of clinically significant muscle weakness (11–36% of the patients) (29–31). One study showed that only patients who were on *both* systemic glucocorticoids and neuromuscular blocking agents developed myopathy, but not those who were on only IV systemic glucocorticoid (41% vs. 0%) (30). Two studies reported the muscle weakness to be systemic (29,30), and one study reported the weakness in both distal and proximal

muscles (30). Both nerve conduction studies (29,30) and needle EMG (29–31) reported some impairments with myopathic patterns (29–31).

Evidence from muscle biopsies showed type II muscle fiber atrophy in some patients with clinically significant muscle weakness (29,30). Acute myonecrosis was noted in some patients with clinically significant muscle weakness in one study (30); and rhabdomyolysis or muscle cell vacuolation in another study (29).

The relationship between the characteristics of glucocorticoid use and myopathy in people with asthma

Studies examining the correlations between the type, dosage, and duration of glucocorticoid use and development of the myopathy are summarized in Table 6. One study reported a “good” correlation between maximal inspiratory pressure and dosage of glucocorticoid use (the *r*- and *p*-values were not reported) (16). In a multiple regression analysis, dosage of glucocorticoids was found to be the only significant predictor of inspiratory muscle *endurance* in one study (*p* = .01) (26).

Table 6. The relationships between glucocorticoids and respiratory and limb muscles in the nine studies.

Glucocorticoid-dependent asthma		
Lower in people with asthma on oral glucocorticoids When comparing to asthma control		
	Significant	Nonsignificant
Respiratory muscles:		
Inspiratory muscle strength	X (27)	X (24,26)
Inspiratory muscle endurance	X (26)	X (24)
Expiratory muscle strength		X (24,27)
Limb muscle:		
Deltoid muscle strength		X (24)
Negative correlations with dosage of oral glucocorticoids		
	Significant	Nonsignificant
Respiratory muscle:		
Inspiratory muscle strength	X (16)	X (24,25)
Inspiratory muscle endurance	X (26)	X (24,25)
Inspiratory muscle fatigability		X (25)
Expiratory muscle strength		X (24,25)
Limb muscle:		
Hip flexor strength	X (16)	
Deltoid muscle size		X (24)
Deltoid and knee extensor strength		X (24,25)
Urine and serum markers of muscle damage		X (16)
Negative correlations with duration of oral glucocorticoids		
	Significant	Nonsignificant
Respiratory muscle:		
Inspiratory muscle strength, endurance, fatigability		X (25)
Expiratory muscle strength		X (25)
Limb muscle:		
Knee extensor strength		X (25)
Deltoid muscle size		X (24)
NON-glucocorticoid-dependent asthma		
Lower in people with asthma on inhaled glucocorticoids When comparing to healthy controls		
	Significant	Nonsignificant
Respiratory muscle:		
Inspiratory muscle strength		X (26,27)
Inspiratory muscle endurance		X (26)
ACUTE exacerbation requiring critical care admission for mechanical ventilation		
Correlations with type of IV glucocorticoids		
	Significant	Nonsignificant
Clinically significant muscle weakness		X (29)
Correlations with dosage of IV glucocorticoids		
	Significant	Nonsignificant
Clinically significant muscle weakness		X (29–31)
Serum creatine kinase elevation		X (29)

Nevertheless, other studies did not find any significant correlations among dosage of glucocorticoid use and *inspiratory* muscle strength, endurance, fatigability (24,25,28), or *expiratory* muscle strength (24,25).

For the limb muscles, one study reported that people with glucocorticoid-dependent asthma taking higher dose of systemic glucocorticoids (≥ 40 mg average daily dose estimated from doses of oral glucocorticoids taken for 2–3 months before the study) had weaker hip flexors than those on lower dose of systemic glucocorticoids (< 40 mg average daily dose) ($p < .05$) (16). Nevertheless, two studies did not find any significant correlations between dosage of oral glucocorticoid use and deltoid muscle size (in a biopsy study), and strength of deltoid and knee extensor

muscles (24,25). There were also no significant correlations between dosage of systemic glucocorticoid use and urine and serum markers of muscle damage (16). In terms of *duration* of glucocorticoid use, two studies showed nonsignificant correlations with inspiratory and expiratory muscle strength, inspiratory accessory muscle endurance/fatigability, quadriceps muscle strength (25); and deltoid muscle size (in a biopsy study) (24). There were also nonsignificant correlations between the product of dosage and duration of glucocorticoid use and inspiratory and expiratory muscle strength, inspiratory accessory muscle endurance/fatigability, quadriceps muscle strength (25).

There were no significant correlations among clinically significant muscle weakness or serum creatine

kinase elevation, and *type* or *dosage* of IV glucocorticoids for patients with acute asthma exacerbation (29–31).

Discussion

Based on the findings of this systematic review, we noted that a number of methods had been used to detect myopathy; the most commonly used measures were respiratory and limb muscle strength, as well as muscle biopsy. Although there is pathophysiological basis for glucocorticoid-induced myopathy, the evidence is inconclusive on the adverse effects of glucocorticoid use on skeletal muscle in people with asthma. There are also inconsistent results on the associations between the type, dosage and duration of glucocorticoid use, and myopathy. Cross-sectional study design constituted most of the studies in this review, which can only *infer* causation and thus may not be the most effective study design to explore the adverse effects of glucocorticoids on muscles in asthma. Future studies with a cohort study design, measuring the cumulative dosage of glucocorticoid use, and integrating possible confounding variables (e.g. physical activity level, nutritional status, and smoking history) (35–37) in the analysis are recommended to further address this question.

Inspiratory and expiratory muscle strength were the most common methods to detect glucocorticoid-induced myopathy in asthma. Respiratory muscle strength is an important outcome for people with asthma. If glucocorticoids have an adverse effect on the respiratory muscle strength, their use may lead to further decline in the respiratory muscle function resulting in more dyspnea and respiratory muscle fatigue (38), which in turn, may be a limiting factor for exercise capacity (37). A better understanding of the effect of glucocorticoid on respiratory muscle function and the characteristics of glucocorticoid use in asthma will help guiding the assessment and interventions of respiratory muscle training and pulmonary rehabilitation for people with asthma who are at high risk of developing respiratory muscle weakness (39,40).

Myopathy has been described to be more commonly associated with the use of fluorinated glucocorticoids, compared to non-fluorinated glucocorticoids (15,20,41). Fluorine substitution of a drug molecule can improve the potency, stability, and the interaction of the drug with its pharmacological target, which improves the bioavailability of the drug (42–44). However, in a study on patients with acute asthma exacerbation where very high doses of glucocorticoids were taken (160–200 mg methylprednisolone or equivalent—equivalent to 200–250 mg of prednisone or equivalent), the type of glucocorticoids

(fluorinated versus nonfluorinated) use did not appear to be predictive of subsequent myopathy (29). It appears that when given at massive doses (20–25 times of dosage of glucocorticoids that is considered high dose) both fluorinated and non-fluorinated glucocorticoids may have similar effects.

More than 10 mg average daily dose of prednisone or equivalent is typically considered a high dose of glucocorticoids and is associated with myopathy (3,41). It is unclear whether inhaled glucocorticoids and any specific dose are associated with myopathy. Two studies in this review did not find any differences in respiratory and limb muscle strength, or inspiratory muscle endurance, between people with glucocorticoid-dependent asthma taking ≥ 10 mg average daily dose of prednisone or equivalent and asthma controls (24,28). Also, even with massive dose of systemic glucocorticoids (20–25 times of the threshold), only about one-third of patients with acute asthma exacerbation developed clinically significant muscle weakness (29–31). The methods used to calculate the dosage of glucocorticoids are important to note. Since only five studies in this review reported the way they calculated the dosage of glucocorticoids, and the method varied among those studies, it is difficult to incorporate this factor in our analysis. It would be more effective to calculate the average daily dose using the daily dose over several months or longer, although this needs to be balanced with the practical difficulties as the dosage of glucocorticoids may be adjusted frequently. Even more difficult would be to incorporate inhaled glucocorticoid use in asthma treatment, as the bioequivalence to oral glucocorticoid is not well known, and the systemic effects among the inhaled glucocorticoids are varied.

A high dose of glucocorticoid for a short duration may be associated with immediate and/or delayed side-effects. In recent studies investigating the adverse effects of oral glucocorticoids burst therapy, which showed increased rates of sepsis (45,46), venous thromboembolism (45), GI bleeding (46), heart failure (46), and fracture (45) were found within 30 days of drug initiation, however, no adverse effects of systematic glucocorticoid burst therapy on muscle structure or function were described. A low dose of glucocorticoid use for a long duration can also cause cumulative adverse effects (47). Hence, focusing on the cumulative dosage of glucocorticoid use may be more productive when exploring the adverse side-effects associated with glucocorticoid use in people with chronic lung diseases (47,48). In a study on glucocorticoid-induced myopathy in people with cystic fibrosis, the cumulative dose of glucocorticoids was an independent predictor of quadriceps atrophy (49).

One study from this review explored the calculated product of dosage and duration of glucocorticoid use and respiratory and limb muscle function but no significant correlations between the variables were observed (25). However, it is unknown how duration of glucocorticoid use was collected in this study (i.e. duration over the study period vs. over a lifetime).

In terms of the methodologic quality of studies in this systematic review, although seven of them were rated as either fair or good, most studies did not provide information on the sample size justification. Without this information, it is difficult to determine if the studies were statistically powerful enough to determine the differences among study groups or the correlations among variables. Also, without adjusting for confounding factors (e.g. physical activity level, nutritional status, and smoking history) (35–37) it is impossible to generate firmer conclusions in the relationship between glucocorticoid use and myopathy.

We have identified several knowledge gaps in the literature on glucocorticoid-induced myopathy in asthma. Various aspects of muscle function, e.g. muscle strength, endurance, fatigability, and broader definitions of limb muscle strength, have been explored. However, there does not appear to be one accepted operational definition of myopathy in these studies. Similar to the criteria for defining sarcopenia, Minetto and colleagues suggested that it would be beneficial to use a *combination* of methods to detect glucocorticoid-induced myopathy, including muscle mass, strength, and performance (50). In future studies on glucocorticoid-induced myopathy in asthma, noninvasive testing for respiratory and/or limb muscle size and muscle quality; muscle strength testing with dynamometry; as well as functional performance assessments like the Short Physical Performance Battery, usual gait speed measurement, or stair climb power test, are recommended to be incorporated into the methods to detect myopathy (49,50). Such a definition is needed to guide the methods used to explore glucocorticoid-induced myopathy in asthma and allow for comparisons and synthesis of results among studies and in clinical practice.

Moreover, despite the wide variety of methods used to detect myopathy in the literature, no studies have explored the associations between glucocorticoid use and changes in muscle *morphological size* and/or *muscle quality* from glucocorticoids in people with asthma. The limb muscle echogenicity, assessed by ultrasonography, was found to be significantly higher (i.e. more fat and scar tissues in the muscle, and hence poorer muscle quality) in people with glucocorticoid-induced myopathy than those without myopathy in a study assessing those with Cushing's disease (51).

Furthermore, several questions about glucocorticoid-induced myopathy in asthma require future study. For example, whether there are differential adverse effects of systemic glucocorticoids on limb versus respiratory muscles; whether there are differential adverse effects on the various aspects of muscle function with the systemic glucocorticoids; whether high dose of inhaled glucocorticoids for a long duration has adverse effects on muscle size and function; and whether systemic glucocorticoid (burst) therapy—high dose for a short duration, has adverse effects on muscle size and function. In addition, even though most of the studies included in this review explored the association between myopathy and *average daily dosage* of glucocorticoid use, studies on the associations of *type*, *duration* or *cumulative dose* of glucocorticoid use are still limited. Also, the *method to calculate* the average daily dose of glucocorticoid use should be standardized.

Given that many questions regarding the adverse effects of glucocorticoids on muscles have not been adequately addressed, future studies are needed to guide assessment and treatment of muscle impairment for people with asthma who are at high risk of glucocorticoids-induced myopathy.

At this point in time, the evidence is still inconclusive on the adverse effects of glucocorticoid use on skeletal muscle in people with asthma. Some studies demonstrated an association between glucocorticoid use and myopathy, which may lead to considerable morbidity. This highlights the importance of adopting the strategies recommended by GINA, when treating patients with asthma, including identifying modifiable risk factors with respect to asthma control (e.g. smoking, inhaler technique, treatment adherence, and food allergies); considering non-pharmacological interventions, (e.g. smoke cessation; physical exercise; avoidance of occupational sensitizers, indoor allergens, and medications that may worsen asthma, e.g. beta-blockers, aspirin, non-steroidal anti-inflammatory drugs; healthy diet; and breathing exercises), and steroid-sparing strategies (e.g. the use of anti-interleukin-5 therapy) (52). If systemic glucocorticoids are deemed necessary, it is important to explain the potential adverse effects to the patients and/or their caregivers, to step down on asthma treatment once good asthma control has been achieved and maintained (52), and to advise patients to engage in physical exercise and other non-pharmacological interventions, although the benefits of exercise training to minimize glucocorticoid-induced myopathy has only been shown in studies with rats (53), and post-heart transplantation (54).

Several limitations are noted in studies included in this review. Key information such as the duration of glucocorticoid use, the method to calculate the average daily dose of glucocorticoids was inconsistently reported in the studies included in this review. Moreover, all studies examining the effects of glucocorticoids on myopathy used a cross-sectional study design, which, has the problem of differentiating the exposure preceding the outcome from simple association (55). This is especially possible when many potential confounding factors, e.g. coexisting medical diseases/conditions, that may also be associated with muscle impairments, such as diabetes (56) or chronic obstructive pulmonary disease (57), were not excluded or factored into the analysis. Also, one main reason why people with asthma are prescribed systemic glucocorticoids or use higher dosage of inhaled glucocorticoids is that they had relatively more severe lung problems, this introduces an important confounder when studying the adverse effects of glucocorticoid use in people with glucocorticoid-dependent asthma versus asthma controls (24,27). Moreover, people with glucocorticoid-dependent asthma in studies in this review had severe asthma, as inferred from the high dose of glucocorticoids they were using. It is difficult to generalize the results to other people with glucocorticoid-dependent asthma with less severe asthma and are on lower dose of oral glucocorticoids.

A cohort study design, instead, may better demonstrate the relationship between the exposure (i.e. glucocorticoid use) preceding the “outcome” (i.e. myopathy) (55), when integrating the potential confounding variables such as physical activity, nutritional status, smoking history (35–37), airway obstruction and hyperinflation (24,26–28), and coexisting diseases/conditions using a multivariable regression analysis.

Conclusions

In conclusion, we only found a small number of studies on glucocorticoid-induced myopathy in people with asthma, using various methods to detect myopathy. Research is needed to determine the operational definition of myopathy, particularly to aid future study in drug-induced muscle impairments. At this stage, it is still unclear if people with glucocorticoid-dependent asthma taking systemic glucocorticoids tend to develop myopathy. The associations between specific type (fluorinated vs. non-fluorinated), route of administration (oral vs. inhaled), dosage, and duration of glucocorticoids and myopathy require further investigation. We recommended using a cohort study design, measuring the cumulative dosage of glucocorticoid use, and

integrating all potential confounding factors in the analysis in future studies of glucocorticoid-induced myopathy, and the underlying characteristics of glucocorticoids (type, route of administration, dosage, and duration) associated with myopathy.

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Declaration of interest

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Table 1S. Keywords used in the literature search.

Myopathy-related		Glucocorticoids-related		Asthma-related
Arm	AND	Adrenal cortex hormones	AND	Aspergillosis
or		or		or
Atrophy		Beclomethasone		Asthma
or		or		
Biceps		Betamethasone		
or		or		
Cachexia		Budesonide		
or		or		
Deltoid		Budesonide plus formoterol		
or		or		
Diaphragm		Ciclesonide		
or		or		
Expiratory		Corticosteroid		
or		or		
Grip		Cortisone		
or		or		
Hamstring		Dexamethasone		
or		or		
Hand		Fludrocortisone		
or		or		

Myopathy-related	Glucocorticoids-related	Asthma-related
Inspiratory	Flunisolide	
or	or	
Lean body weight	Fluticasone	
or	or	
Leg	Glucocorticoids	
or	or	
Limb	Glucocorticosteroid	
or	or	
Lower extremity	Hydrocortisone	
or	or	
Muscles	Methylprednisolone	
or	or	
Fatigue	Mometasone	
or	or	
Force	Prednisolone	
or	or	
Growth	Prednisone	
or	or	
Hypertrophy	Steroids	
or	or	
Hypotrophy	Triamcinolone	

Myopathy-related	Glucocorticoids-related	Asthma-related
or		
Mass		
or		
Strength		
or		
Myopathy		
or		
Peripheral		
or		
Pinch		
or		
Power		
or		
Quadriceps		
or		
Rectus femoris		
or		
Respiratory		
or		
Shoulder		
or		

Myopathy-related	Glucocorticoids-related	Asthma-related
Size		
or		
Skeletal		
or		
Striated		
or		
Thickness		
or		
Torque		
or		
Triceps		
or		
Vastus		
or		
Wasting		
or		
Weakness		