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Clinical perspectives on myopathic complications in nephropathic cystinosis

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Abstract

Patients with nephropathic cystinosis are now living into their 50s and beyond thanks to advances in medical management. Due to this shift in the natural history of the disease, monitoring for and addressing extrarenal manifestations, including myopathy, has emerged as an area of increasing importance. Muscle involvement typically begins before the onset of noticeable symptoms, and evidence suggests that subtle signs may even emerge in childhood. The origin of muscle involvement in cystinosis has not fully been elucidated and is likely multifactorial. Nonetheless, cellular toxicity due to intralysosomal cystine accumulation appears to be a key catalyst. Myopathy in cystinosis, which can lead to muscle weakness, dysphagia, and pulmonary dysfunction, contributes to significant morbidity and mortality, including impaired quality of life, reduced ability to independently perform activities of daily living, feeding difficulties and malnutrition, choking, and aspiration. Nephrologists typically act as the de facto primary cystinosis providers and are tasked with screening for muscle involvement and coordinating multispecialty referrals to neurology, pulmonology, gastroenterology, and physical, occupational, and speech therapy. In this review, we aim to summarize the current understanding of myopathy in nephropathic cystinosis and discuss strategies to support monitoring, assessment, management, and mitigation of this complication, as well as specialist referral and coordination.

Keywords Cysteamine, Cystinosis, Dysphagia, Lysosomal storage disorder, Myopathy, Pulmonary dysfunction

Introduction

Cystinosis is a rare autosomal recessive lysosomal storage disorder affecting approximately 1 in 100,000 to 200,000 live births [1]. Genetic variants in *CTNS*, encoding for the cystinosin transporter protein, lead to continuous cystine accumulation within lysosomes and consequent multiorgan damage [1]. Cystinosis is classified into three clinical subtypes—nephropathic (infantile) cystinosis, intermediate (juvenile/late-onset) cystinosis, and non-nephropathic (ocular) cystinosis—primarily based on disease severity and age at symptom onset; although the disease is present in the individual from birth, symptoms emerge at various points in time [2]. Nephropathic cystinosis is the most common form of the disease [2]. Symptoms of Fanconi syndrome typically emerge in the first year of life for patients with nephropathic cystinosis, with nearly all eventually developing kidney failure and requiring dialysis and/or transplantation [1, 2]. In late adolescence and adulthood, patients progress to a phenotype dominated by extrarenal complications [1]. The term "cystinosis" will be used instead of "nephropathic cystinosis" from this point forward, as this simplifcation is commonly used within the cystinosis literature due to the rarity of the other disease subtypes.

Cystinosis treatment involves supportive therapies to address renal and extrarenal complications and oral and ophthalmic cysteamine, the only available disease-modifying therapies, to deplete intralysosomal cystine [2]. Early and sustained oral cysteamine use has been associated with delayed time to kidney failure and reduced incidence of extrarenal complications that are associated

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with myopathy, including muscle weakness, dysphagia, and pulmonary dysfunction [3–5]. Due to the growing recognition of the impact of myopathy in cystinosis on morbidity and mortality, this paper aims to comprehensively review the current understanding and offer approaches to support routine monitoring and management in these patients.

Overview of muscle involvement in cystinosis

Myopathy is a common extrarenal complication of cystinosis, leading to muscle weakness, dysphagia, and respiratory dysfunction [6]. Muscle involvement begins before clinically overt symptoms emerge, and in some cases, muscle strength may be preserved until later stages of myopathy [6, 7]. The clinical presentation often starts with weakness and wasting of the distal upper extremities, which may be accompanied by dysphagia. Over time, myopathy becomes more generalized, with proximal muscle involvement and respiratory muscle weakness [8–10]. Although myopathy has historically been viewed as a late complication of cystinosis, early signs of potential muscle dysfunction, such as hypotonia, swallowing/feeding difficulties, and speech changes, have been described by Trauner et al. [11] and Elenberg et al. [12] in younger patients.

Pathophysiology

The underlying etiology of myopathy in cystinosis is not well understood; however, toxicity from intralysosomal cystine accumulation may play an important role in pathomechanism (Fig. 1) [8, 10, 13, 14]. Skeletal muscle biopsies in patients with cystinosis have revealed high cystine concentrations and abundant autophagic vacuoles in muscle cells as well as significant variability in muscle fiber size, atrophy of slow-twitch fibers, and presence of ring fibers [8–10]. Higher muscle cystine concentrations have been found to be associated with greater muscle involvement, especially as time off cysteamine therapy increases [4, 9, 15].

Despite its ability to reduce muscle cystine levels and exert a potential benefit on muscle-related complications, cysteamine is not able to fully override the myopathic process, leading researchers to suspect a multifactorial origin beyond cystine accumulation [6, 22]. There is mounting evidence to support the roles of mitochondrial dysfunction, impaired autophagy, and increased oxidative stress due to loss of functional cystinosin in the development of myopathy in patients with cystinosis; however, further studies are needed to elucidate this hypothesis [16, 18]. Other possible causes, including hypothyroidism and chronic kidney disease (CKD), are less likely to explain the full clinical picture of myopathy in patients with cystinosis while contributions from immunosuppressant use and carnitine deficiency cannot be completely ruled out due to limited evidence [6, 9, 17, 22]. Furthermore, myopathy and other disease sequelae, including gastrointestinal (GI) distress, skeletal abnormalities, and neurologic impairment, share overlapping symptoms, making it even more difficult to parse the underlying etiology [11, 23, 24].

The impact of myopathy and need for comprehensive care

Myopathy in cystinosis has far-reaching implications, negatively affecting patients' quality of life and ability to independently perform activities of daily living (ADLs) [6, 14]. Because patients with cystinosis are living longer, dysphagia and pulmonary dysfunction, potentially leading to choking, aspiration, and respiratory infections, are increasingly being identified as important contributors to death in this disease [3–5, 10, 21]. Swallowing and feeding difficulties can also exacerbate impaired growth, poor weight gain, and malnutrition—complications already prevalent and concerning in patients with this disease [12]. Additionally, distal muscle weakness and dysphagia can impact patients' ability to manage the high pill burden of their daily treatment regimen, in particular, cysteamine and immunosuppressants; patients may have difficulty opening capsules/packets and swallowing oral medications safely multiple times per day [5, 6, 25].

Comprehensive cystinosis management requires a multidisciplinary approach, with the patient's nephrologist, primary care provider, or geneticist often assuming the role of "care quarterback," or primary cystinosis provider [19]. Monitoring for muscle involvement is largely reliant on patient-reported symptoms, which should be assessed at each clinic visit or as appropriate [19]. If muscle involvement is suspected, referral to specialists, including neuromuscular specialists, gastroenterologists, pulmonologists, and physical, occupational, and speech therapists, is warranted for further assessment and management [26, 27].

Due to the progressive and chronic nature of the disease, patients with cystinosis often experience treatment burnout or periods when they become disengaged from their care [28]. Maintaining motivation to actively participate in care can become particularly challenging as patients reach adolescence and adulthood, a time that coincides with increasing responsibilities, life changes, and multisystem involvement, including myopathy [19, 28]. Clinicians should consider the physical and psychosocial burden of comorbidities, along with the challenges associated with additional specialist visits and therapies, and provide individualized support to patients as needed [28]. Specialized clinics for the treatment of neuromuscular disorders, such as muscular dystrophy, incorporate a multidisciplinary approach

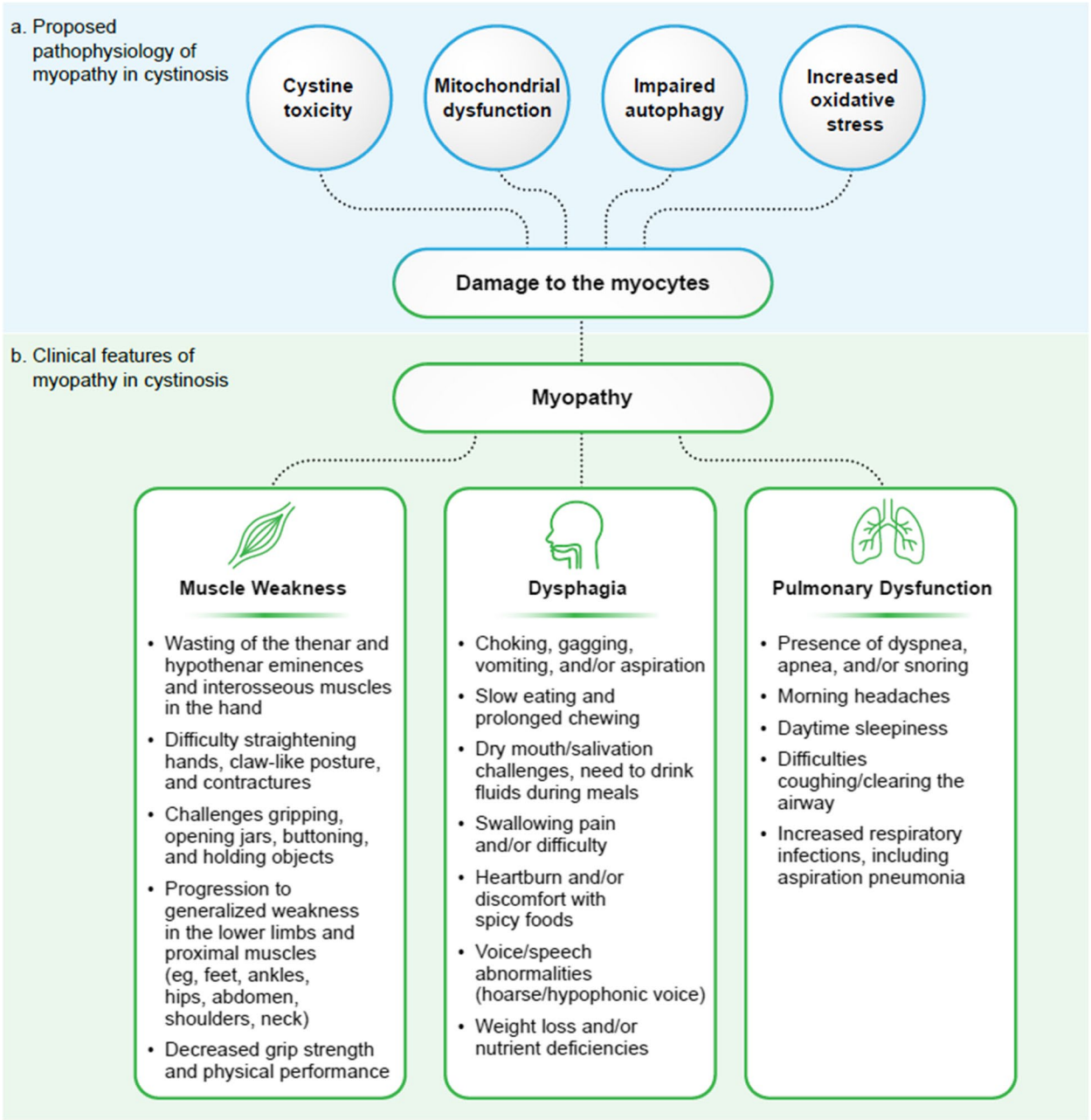

Fig. 1 Proposed mechanisms and clinical features of myopathy in cystinosis. **a** Cystine toxicity, mitochondrial dysfunction, impaired autophagy, and increased oxidative stress contribute to the development of myopathy in cystinosis. **b** Clinical features of myopathy in cystinosis include muscle weakness, dysphagia, and pulmonary dysfunction [5, 6, 8–12, 14, 16–22]

to provide comprehensive myopathy care [29]. Where available, referral of patients with cystinosis and muscle involvement to such clinics may help alleviate the burden of coordinating multiple specialist appointments and ensuring communication among providers. Clinicians should also identify opportunities to implement strategies to support patients where appropriate, including encouraging self-management skills in adolescence and early adulthood, routinely employing validated screening tests to monitor psychological well-being and quality of life, initiating referral for additional psychosocial intervention, leveraging motivational interviewing techniques, and offering peer connection and/or mentorship [19, 28].

Muscle weakness in cystinosis

The prevalence of muscle weakness varies across studies, likely resulting from differences in assessment type, patient demographics, and cysteamine availability among older populations [3, 4, 22]. In a study of 100 adults with cystinosis (mean age, 26.2 years) followed by the National Institutes of Health (NIH) Clinical Center from 1985 to 2006, Gahl et al. [4] found evidence of myopathy, defined as clinical wasting of the distal hand muscles, in half of patients. In this study, the 5 patients who had received cysteamine therapy for at least 20 years did not exhibit distal hand muscle wasting, suggesting that long-term treatment may be linked to lower rates or delayed onset of myopathy [4]. In a 2012 study of 86 adults with cystinosis (mean age, 26.7 years) in France, approximately 69% of patients exhibited distal hand muscle atrophy; the incidence of neuromuscular complications was significantly lower in patients who had initiated cysteamine by 5 years of age [3]. A more recent study of 55 children and adults with cystinosis (mean age, 20.7 years) followed from 2018 to 2019 in Germany found mild to severe hand muscle involvement in approximately 44% of patients [22]. In this study, severity of hand weakness was not associated with age at cysteamine initiation or cysteamine non-adherence/discontinuation [22]. A small number of case reports have shown evidence of stabilization or slight improvement of myopathy with good cysteamine adherence [9, 10].

Evidence of muscle disease has been demonstrated in patients before the appearance of clinically noticeable muscle weakness [6, 7, 10, 15]. Overt myopathy typically begins with wasting and weakness in the hands, wrists, and forearms, with muscles between the metacarpals (interosseous muscles) and those controlling the thumb and fifth digit movements (thenar and hypothenar eminences, respectively) particularly affected [6, 8, 9, 20]. Sadjadi et al. [6] aimed to characterize muscle involvement in 20 adults with cystinosis (mean age, 31 years; age range, 20–64 years) and found that 85% self-reported some degree of limb weakness. Upon examination, patients were found to have weakness of intrinsic hand muscles and wrist/elbow flexion and extension; 3 patients were found to have hand contractures [6]. Additionally, decreased grip strength has been reported in children and adults with cystinosis [17]. Patients with distal myopathy may have challenges straightening their hands, which often assume a claw-like position, and have difficulty with ADLs such as gripping, opening jars, and buttoning clothing (Fig. 1) [6, 8, 9, 20].

Patients with distal myopathy may experience weakness in the lower extremities; however, this is less commonly seen in early myopathic stages [6]. In the study by Sadjadi et al. [6], most patients (17/20) had distal upper extremity weakness, whereas only 2 patients exhibited distal lower extremity weakness. Myopathy tends to become more generalized as it progresses, leading to weakness in lower limb and proximal muscles, including those in the feet, ankles, hips, abdomen, shoulders, and neck [6, 8, 22]. Additionally, patients with cystinosis may experience overall weakness and reduced muscle function [22]. In a cross-sectional study of 55 patients with cystinosis (mean age, 20.7 years), physical performance, measured via two-legged jump test, was found to be 27% to 92% (mean, 64%) lower than healthy age- and sex-matched controls [22]. Patients with lower white blood cell (WBC) cystine levels were found to have significantly better physical performance on the jump test than patients with higher WBC cystine levels [22].

Monitoring and assessment

International consensus–based guidance from Levtchenko et al. [19] emphasizes the importance of clinical history and patient report in monitoring for muscle involvement in cystinosis. During routine clinic visits, it is recommended that primary cystinosis providers ask patients and/or caregivers about ambulation challenges, extremity dysfunction, and difficulties with ADLs. Hand-grip strength, measured via dynamometry, is often decreased in patients with cystinosis [17] and could be used to aid in monitoring for muscle-strength changes. To assess for upper and lower extremity dysfunction, Sadjadi et al. [6] developed the Distal Myopathy Function Scale (DMFS), a 22-item survey based on feedback from the cystinosis community and experience in similar disease states. In 20 adults with cystinosis (mean age, 31 years; age range, 20–64 years), the DMFS was found to have relatively good reliability, sensitivity, stability, and unidimensionality and may be useful in this patient population, although additional studies are needed [6].

If muscle weakness is suspected, referral to a neurologist with experience in neuromuscular disorders is warranted for evaluation, including assessment of muscle weakness, electromyography, neurophysiology, and mobility/endurance testing [6, 19, 22]. Muscle biopsy is not recommended, as the underlying histopathology is already well described and there is little clinical utility (Table 1) [19].

Management and mitigation strategies

Since cysteamine is the only currently available disease-modifying treatment, early and continuous therapy is recommended for all patients with cystinosis [3, 4]. In patients with myopathy who are untreated or undertreated, cysteamine therapy may still provide a benefit [9, 10]. WBC cystine levels should be monitored routinely to assess the adequacy of short-term cystine tissue

Table 1 Monitoring/screening and management/mitigation for muscle weakness in patients with cystinosis

Monitoring/screening	• During routine visits, ask patients about functional changes and/or challenges [19] • Questions to consider asking include o Have you experienced changes in how you move and/or walk? o Has there been a decrease in your physical activity? o Do you often drop objects? o Have you noticed difficulties opening jars, picking up items, or buttoning clothing? o Is it challenging for you to prepare or take your medications? • If appropriate, implement routine dynamometry to monitor for changes in hand grip strength [17] • Routinely monitor WBC cystine levels to assess cysteamine adherence and inform dosage adjustments [30] • Refer patients to a neurologist with experience in neuromuscular disorders if muscle weakness is suspected [6, 19, 22] o Muscle biopsy is not recommended [19] • Consider implementation of routine screening tools to identify the need for psychosocial support [19]
Management strategies	• Ensure patients receive early and continuous cysteamine therapy [3, 4] o Explore potential barriers to taking cysteamine as prescribed in patients who are undertreated/not at target WBC cystine levels o Consider restarting cysteamine in patients who have stopped treatment • Consider referral to physical and/or occupational therapists with experience in muscle disease for evaluation and implementation of an appropriate exercise regimen [19, 26] • Consider referral to physical/occupational therapists, physiatrists, and/or orthopedists, who may consider or implement [23, 26]: o Orthotics o Mobility aids o Adaptive equipment • Consider referral to mental health specialists or social workers for additional support in patients who are experiencing psychological distress or impaired well-being/quality of life [19] • Optimize bone and hormone health[a] [17, 23, 31, 32] • Monitor plasma carnitine levels to ensure appropriate supplementation [33] • Consider adding coenzyme Q10 and/or B vitamins to regimens for appropriate patients[b] [34, 35]

WBC white blood cell

[a] See international consensus guidelines from Hohenfellner et al. [23] for optimizing bone and hormone health

[b] These supplements are prescribed for other types of myopathy; there have been no studies to evaluate the effects of these supplements on myopathy in cystinosis specifically [34, 35]

depletion, optimize medication dosage, and evaluate adherence [30].

Aside from altering the underlying disease process with cysteamine, the management of myopathy is largely supportive, with aims of improving overall strength, limiting the progression of the disease, and maximizing patients' functional abilities and quality of life (Table 1) [26]. It can be helpful to refer patients to physical and/or occupational therapists with experience in muscle disease for initial evaluation and implementation of an appropriate exercise regimen, with subsequent assessments and adjustments as needed [19, 26]. In patients with cystinosis, aerobic and flexibility-type activities have been associated with improved grip strength [17]. Although a significant association between strength-building exercises and grip strength was not found, Iyob-Tessema et al. [17] suggested that strength-training exercises may still benefit patients with cystinosis. If appropriate, it is generally recommended that patients with cystinosis participate in regular physical activity to enrich overall health, improve pulmonary function, support bone strength, and enhance well-being [17, 19, 23, 26]. Patients may find value in keeping a daily journal to further understand the personal impact of exercise [26]. In addition to incorporating routine physical activity, clinicians can encourage patients to consider lifestyle modifications that are known to positively influence overall well-being, such as eating a balanced diet and avoiding dehydration [19]. Although not specific to cystinosis, recommendations for general myopathy management include the use of orthotics, mobility aids, and adaptive equipment [26]. For patients in whom these strategies may be beneficial, referrals to appropriate specialists, such as physical/occupational therapists, physiatrists, and/or orthopedists, are warranted [23, 26].

Further interventions to support muscle health in patients with cystinosis include optimizing bone and hormone health and strategic supplementation [17, 23, 31, 32]. International expert recommendations for managing cystinosis metabolic bone disease include replacing urinary losses due to Fanconi syndrome, correcting vitamin D and parathyroid hormone levels, initiating growth hormone, and identifying the need for testosterone replacement in male patients [23]. Male patients with cystinosis have been found to have impaired grip strength, possibly related to hypogonadism with consequent low testosterone levels [17]. Although there have not been controlled studies on the impact of testosterone replacement or alternative therapies on myopathy in male patients, it is

recommended to routinely assess hormone levels and consider referral to an endocrinologist as needed [23, 32].

Carnitine is typically supplemented in patients with cystinosis due to high renal losses and potential for deficiency with Fanconi syndrome; it is often continued even after kidney transplant [22, 33, 36]. In a small study of 5 pediatric patients with cystinosis (age range, 2–18 years), Besouw et al. [33] found that daily L-carnitine at 50 mg/kg resulted in over-supplementation, with normal plasma-free carnitine levels and elevated urine carnitine derivatives. When supplementation was stopped, however, plasma-free and total carnitine levels decreased, indicating a potential need for ongoing supplementation [33]. The authors recommended monitoring plasma carnitine profiles to optimize dosing and avoid over-supplementation in patients with cystinosis [33]. Although carnitine is considered safe, it is advisable to use caution when prescribing high doses, as the long-term effects are unknown [33]. In addition to carnitine, coenzyme Q10 and B vitamins may support mitochondrial function, and they have been prescribed for other types of myopathy, such as statin-induced and mitochondrial myopathies [34, 35]. There are, however, no studies evaluating their effects on myopathy in cystinosis specifically. It is recommended to use caution when prescribing supplements to patients with compromised kidney function.

Swallowing and oral motor dysfunction

The prevalence of swallowing impairment and oral motor dysfunction is variable across studies, ranging from as few as 2% and as many as >80% of patients; despite its variability, several studies report rates closer to 50% [3–5, 11, 12, 14, 37]. In a study of 101 children and adults with cystinosis (mean age, 28.2 years) followed at the NIH Clinical Center between 1987 and 2004, approximately 74% self-reported a history of swallowing abnormalities [5]. In this study, swallowing examination via videofluoroscopic swallow study (VFSS), also known as modified barium swallow study, found dysfunction in the oral, pharyngeal, and esophageal phases of swallowing in 24%, 51%, and 73% of patients, respectively [5]. To determine the potential impact of cysteamine on dysphagia, swallowing severity and oral muscle composite scores were assessed in correlation with the number of years without oral cysteamine; both scores were significantly worse the longer patients were not on therapy [5]. Conversely, scores were significantly better the longer patients were on cysteamine treatment [5]. In a study of 13 posttransplant, cysteamine-naive patients, Charnas et al. [9] found possible evidence of stabilization of dysphagia with cysteamine therapy. Out of 7 patients followed for ≥3 years, the 2 patients with the lowest cysteamine adherence developed significant swallowing dysfunction and clinically obvious distal weakness and wasting, whereas the 2 patients with incomplete adherence exhibited only mild increases in dysphagia and distal muscle wasting [9]. There was no mention of disease progression in the 3 patients with excellent cysteamine adherence [9]. At least 1 case report has also described stabilization or slight improvement of swallowing and oral motor function with cysteamine use [10].

Symptoms of dysphagia in patients with cystinosis include choking, gagging, vomiting, slow eating, dry mouth/salivation challenges, swallowing pain and/or difficulty, heartburn, and discomfort with spicy foods [5, 11, 22]. Additionally, patients may experience increased difficulty swallowing solid food versus liquids (Fig. 2) and the need to drink large quantities of fluids to help with swallowing during meals [12, 27, 38]. Abnormalities have been reported in all phases of swallowing and include needing additional chewing, challenges with tongue control, pooling of saliva over the vocal cords, and laryngeal penetration and aspiration [5, 14, 22, 27]. Patients with esophageal abnormalities may experience impaired peristalsis, reflux and esophagitis, and delayed release of the lower esophageal sphincter [5]. Voice abnormalities, such as a hoarse or hypophonic voice, have also been reported [8, 11, 12].

Early signs of swallowing abnormalities may be present before overt myopathic symptoms [11]. A study by Trauner et al. [11] of 22 children with cystinosis (age range, 2.3–16.0 years) found high rates of persistent feeding difficulties beginning in early childhood and continuing despite adequate treatment of Fanconi syndrome. Of those who underwent oral-motor testing, most patients (15/18) displayed generalized hypotonia, suggesting the potential involvement of underlying neurologic and neuromuscular dysfunction in feeding difficulties [11]. Elenberg et al. [12] conducted a questionnaire-based study of GI dysfunction in 70 children and adults with cystinosis (53/70 patients were aged ≤16 years) and found that 83% of patients reported episodes of gagging and/or vomiting and 41% reported swallowing difficulties. Additional signs of swallowing impairment in children may include choking, prolonged chewing, the need for additional fluids to swallow, and refusal to swallow [12].

Monitoring and assessment

Routine assessment of clinical history and self-reported symptoms are key to the identification of swallowing dysfunction (Table 2) [19]. Signs and symptoms of dysphagia to be assessed include chewing and/or swallowing difficulties, dry mouth, long mealtimes, the feeling of food and/or pills sticking in the throat, gagging, choking, or vomiting [5, 11, 19]. It may also be helpful to ask about weight loss, increased respiratory infections, and vocal

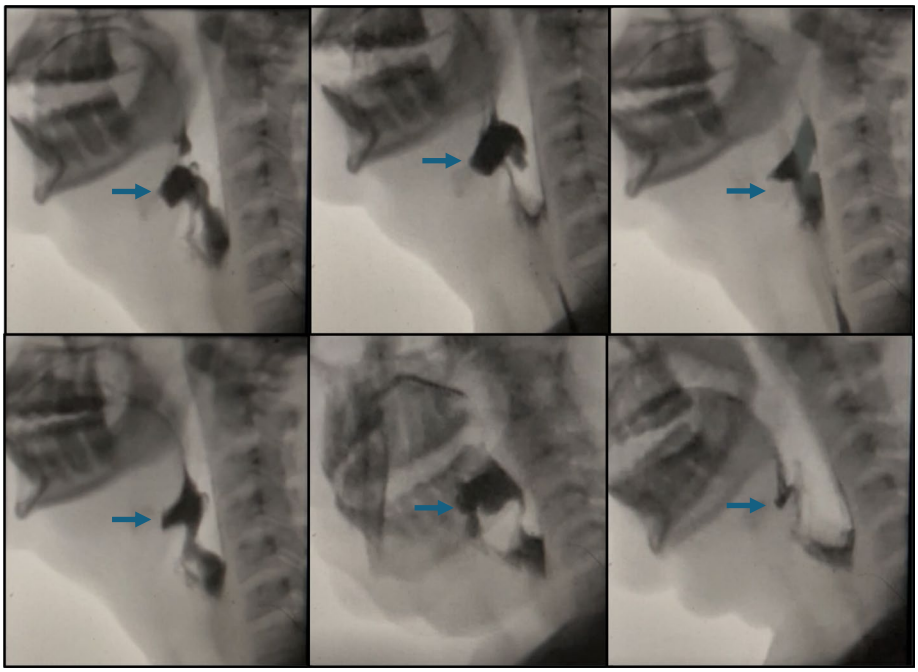

Fig. 2 Videofluoroscopic swallowing study results of a patient with cystinosis. Patient was found to have diffuse pharyngeal weakness and significant residue with several consistencies, which was most pronounced with solid consistencies. Patient takes several attempts to swallow and employs compensatory strategies to complete the swallow. See supplementary information for full video (Additional file 1)

Table 2 Monitoring/screening and management/mitigation for dysphagia in patients with cystinosis

Monitoring/screening	• During routine visits, ask patients about functional changes and/or challenges [19] • Questions to consider asking include o Does it take you a long time to finish meals? o Do you avoid eating certain foods, and why? o Do you feel the need to take sips of fluids after bites of food? o Does it feel like food or pills get stuck in your throat when you swallow? o Do you vomit, choke, or gag when you eat? o Have you recently lost weight? o Have you, or those around you, noticed changes in your voice/speech? o Have you had any recent infections? • Consider using patient questionnaires (e.g., MDADI, EAT-10[a]) [6] • If accessible, consider utilizing swallowing screening tools (e.g., TOMASS, bedside swallow test) to identify oropharyngeal dysfunction[b] [27, 39, 40] • Consider referral to speech language pathologists or gastroenterologists for additional testing [21, 26, 27, 41] • Consider implementation of routine screening tools to identify the need for psychosocial support [19, 42, 43]
Management strategies	• Ensure patients receive early and continuous cysteamine therapy [3, 4] o Explore potential barriers to taking cysteamine as prescribed in patients who are undertreated/not at target WBC cystine levels o Consider restarting cysteamine in patients who have stopped treatment • Consider referral to speech language pathologists, occupational therapists, dietitians, dentists, otolaryngologists, and gastroenterologists for instruction/implementation on [21, 26, 27]: • Nutritional status optimization (Elenberg 1998) • Modifications to food consistency [12] • Appropriate postural compensations (e.g., placing food closer to the back of the tongue, tucking the chin down to chest) [12] • Safe swallowing techniques (e.g., double swallowing boluses, increasing fluid consumption) [12, 21, 27] • Consider gastrostomy tube placement if swallowing becomes unsafe, due to risk of choking and/or aspiration [21] • Consider referral to social workers or mental health specialists for additional support in patients who are experiencing psychological distress or impaired well-being/quality of life due to dysphagia [44]

EAT-10 Eating Assessment Tool, *MDADI* MD Anderson Dysphagia Inventory, *TOMASS* Test of Masticating and Swallowing Solids

[a] MDADI and EAT-10 are not validated in the cystinosis patient population [6]

[b] TOMASS has been validated in children, and experts recommend routine screening of patients with cystinosis, beginning in childhood [27]

changes [11, 19]. Patients may subconsciously develop compensation strategies to manage chewing and swallowing difficulties, which can make it difficult for them to fully realize the extent of dysfunction [26]. Clinicians can help to elicit information on swallowing difficulties by asking carefully selected questions to understand potential dysfunction [19]. Patient questionnaires, such as the MD Anderson Dysphagia Inventory and the 10-item Eating Assessment Tool, have also been used to evaluate the impact and severity of dysphagia in patients with cystinosis, although they have not been validated in this population [6].

Swallowing screening tools, such as the Test of Masticating and Swallowing Solids (TOMASS) and bedside water swallow tests, can be used in the clinical setting to identify dysfunction in the oral and pharyngeal phases of swallowing [27, 39, 40]. The TOMASS is non-invasive, easily implemented in the clinical setting, and has also been validated in children [45]. van Rijssel et al. [27] have suggested using the TOMASS to routinely screen for signs of swallowing dysfunction in patients with cystinosis, beginning in childhood.

If specialist evaluation is warranted, assessment using VFSS is considered the gold standard [27, 41]. Various methods exist to categorize dysfunction on VFSS, including the penetration-aspiration scale (PAS) and Modified Barium Swallow Impairment Profile (MBSImP™), both of which have been used to measure swallowing dysfunction in patients with cystinosis [6, 14, 22, 46]. Based on results from a study of 20 adults with cystinosis (mean age, 31 years; age range, 20–64 years), Sadjadi et al. [6] hypothesized that evaluation of VFSS via PAS may not be sensitive enough to capture dysphagia in this patient population. Indeed, VFSS evaluation by PAS found objective evidence of swallowing dysfunction in only 6/20 (30%) patients, although 60% of patients self-reported difficulties with swallowing [6]. Upon retrospective analysis of these same VFSS data using the MBSImP, rather than PAS, objective evidence of swallowing dysfunction was found in >50% of patients and the analysis better characterized distinct swallowing challenges [14].

Management and mitigation strategies

The treatment of dysphagia is largely focused on preserving nutritional status while minimizing risk of aspiration and associated complications, with referral to speech and occupational therapists, dietitians, dentists, otolaryngologists, and gastroenterologists, as needed (Table 2) [21, 26, 27]. Patients should be instructed on appropriate postural compensations, such as placing food closer to the back of the tongue and tucking the chin down to the chest; modifications to food consistency may be needed, and safe swallowing techniques, including double swallowing boluses and increasing fluid consumption, should be employed [12, 21, 27]. Patients may also require nutritional supplementation to ensure adequate caloric intake [12]. Finally, if dysphagia progresses to the point where it is unsafe for patients to swallow, gastrostomy tube placement should be considered [12].

In a recent publication by Sullivan et al. [47], a 5-week respiratory training program targeting the neck and submandibular muscles was found to improve oral phase dysphagia in 8 patients with cystinosis. In addition to possible improvements from the training program, the authors hypothesized that repeated VFSS along with counseling and education may have led to a positive cognitive behavioral impact that allowed for enhanced swallowing mechanics in this group of patients. As this study was small and did not include a control arm, additional studies are needed to confirm the utility of this type of training program. Though evidence is lacking in patients with cystinosis, the presence of psychological challenges, such as anxiety or fear of choking, has been described in patients with dysphagia in other disease states [42, 43]. Clinicians should be aware of the potential for psychosocial difficulties in patients with cystinosis and dysphagia and consider referral for additional support as appropriate [44].

Respiratory involvement

Despite its common occurrence, little has been published about respiratory involvement in patients with cystinosis. A study by Anikster et al. [48] found pulmonary dysfunction, with decreased functional parameters, in 12 adults with nephropathic cystinosis (age range, 21–40 years) who were admitted to the NIH Clinical Center from 1997 to 1998 and had lived ≥17 years without cysteamine therapy. In this study, pulmonary dysfunction followed a pattern of restrictive lung disease, with reduced total lung capacity (< 80%) in 10/12 patients and decreased FVC, FEV_1, maximal inspiratory pressure (MIP), and mean expiratory pressure (MEP) in those who were tested [48]. Lung parenchyma was normal in most patients (9/11) who underwent chest radiography and computed tomography [48]. In a second study, Gahl et al. [4] identified respiratory involvement in 69% of adults with cystinosis ($n = 77$; mean age, 26.2 years). In this study, pulmonary dysfunction appeared to increase with time off cysteamine and decrease with time on treatment [4]. None of the 4 patients who had taken cysteamine for 21 to 30 years exhibited signs of respiratory involvement [4].

Early signs of respiratory involvement may be limited to shortness of breath during exercise, which might go unnoticed in patients who are not physically active [21]. The progression of pulmonary dysfunction may result in patients experiencing mild dyspnea upon exertion and

eventually having symptoms at rest [21]. Pulmonary dysfunction can affect patients' ability to effectively cough and clear the airway, leading to concerns for aspiration, increased risk of infection and pneumonia, and possible asphyxiation with bolus obstruction [21].

The etiology of respiratory involvement in patients with cystinosis appears to be multifactorial, likely due to respiratory muscle weakness from underlying myopathy and anatomic abnormalities that affect chest configuration and facial structure [13, 48–50]. Patients with cystinosis may experience weakness of the accessory chest muscles, including the diaphragm and the intercostal and abdominal muscles, which are critical for breathing and coughing [21]. Additionally, a conical chest configuration has been reported in adults with cystinosis, likely from Fanconi syndrome and bone involvement in childhood [48, 50]. Following evaluation of 44 children with cystinosis (mean age, 9.94 years), Müller et al. [50] found significant early alterations in chest configuration that were characterized by increased chest depth and varied significantly from age-matched controls with CKD, potentially contributing to the restrictive pattern of pulmonary dysfunction seen in adults with cystinosis.

Monitoring and assessment

In clinical practice, patients with cystinosis should be routinely evaluated for signs and symptoms of respiratory involvement, including the presence of dyspnea/apnea, snoring, morning headaches, daytime sleepiness, decreased coughing capacity, and respiratory infections (Table 3) [19, 21]. Referrals to pulmonologists, respiratory therapists, or comprehensive care clinics with experience in neuromuscular disorders may be warranted, as these clinicians will be aware of specific support that is needed [26].

Pulmonary function testing is indicated on an annual basis in patients with evidence of muscle weakness in non-pulmonary muscles and in patients with dyspnea during exercise or in those with orthopnea [21, 26]. Spirometry and measures of maximal inspiratory pressure and maximal expiratory pressure (MEP) are recommended for detecting respiratory muscle weakness [21, 26, 51]. Arterial blood gas measurement is not sensitive enough to capture early changes in pulmonary function [21]. Further testing may include body plethysmography or gas dilution methods to measure absolute lung volumes and diffusion capacity [21]. Additionally, patients with cystinosis should undergo periodic evaluation for sleep apnea [21].

Table 3 Monitoring/screening and management/mitigation for pulmonary dysfunction in patients with cystinosis

Monitoring/screening	• During routine visits, ask patients about functional changes and/or challenges [19] • Questions to consider asking include o Do you snore when you sleep? o Do you wake up with headaches in the morning? o How tired or out of breath do you feel performing your normal activities during the day? o Do you have trouble taking deep breaths? o Do you feel like your cough is weaker than it used to be? o Have you had any recent respiratory infections? • Consider referrals to pulmonologists, respiratory therapists, or comprehensive care clinics experienced in neuromuscular disorders for further evaluation [26] o Pulmonary function testing, including spirometry and MIP/MEP, is indicated on an annual basis in patients with evidence of non-pulmonary weakness and in patients with dyspnea during exercise or orthopnea [21, 26, 51] • Consider implementation of routine screening tools to identify the need for psychosocial support [19, 42, 43]
Management strategies	• Ensure patients receive early and continuous cysteamine therapy [3–5, 19] o Explore potential barriers to taking cysteamine as prescribed in patients who are undertreated/not at target WBC cystine levels o Consider restarting cysteamine in patients who have stopped treatment • Encourage patients to avoid smoking/vaping and create a smoking cessation plan if needed [21, 26] • Recommend the COVID-19, influenza, pneumococcal, and other vaccines as appropriate, and aggressively treat respiratory infections [21, 26, 52] • Support patients in maintaining a healthy weight [21, 26] • Consider referrals to specialists for consideration/implementation of o Respiratory exercises[a] [25] o Optimization of underlying respiratory conditions (e.g., asthma) [21, 26] o CPAP or BIPAP in patients with sleep apnea [21] o Assisted mechanical ventilation in patients with severe pulmonary dysfunction[b] [21, 26] • Consider referral to social workers or mental health specialists for additional support in patients who are experiencing psychological distress or impaired well-being/quality of life [44]

BIPAP bilevel positive airway pressure, *CPAP* continuous positive airway pressure, *MEP* maximal expiratory pressure, *MIP* maximal inspiratory pressure

[a] A 5-week exercise protocol for patients with cystinosis using an EMST150 (Aspire Products; Gainesville, FL, USA) resulted in positive outcomes; however, additional studies are needed to confirm its effectiveness [25, 53]

[b] Assisted mechanical ventilation should be performed in accordance with the patient's and/or family's wishes [21, 26]

Management and mitigation strategies

The management of pulmonary dysfunction is critical to reduce the risk of aspiration and associated complications and requires a comprehensive care approach with cysteamine therapy, dysphagia management, and interventions aimed at protecting and supporting the airway (Table 3). Patients with cystinosis and severe dysphagia may benefit from respiratory exercises to improve cough strength and potentially protect against aspiration [25]. A 5-week exercise protocol using an EMST150 (Aspire Products,Gainesville, FL, USA), a handheld device designed to employ resistance training to improve the expiratory and submental muscles, was found to significantly improve respiratory outcomes, MEP, and peak cough flow in a study of 20 adults with cystinosis [25, 53]. However, additional confirmatory studies are needed [25, 53]. Sleep apnea treatment typically involves the use of continuous or bilevel positive airway pressure [21]. In patients with cystinosis and severe pulmonary dysfunction, assisted mechanical ventilation may be necessary to prolong life, in accordance with the patient's and/or family's wishes [21, 26]. The use of non-invasive mechanical ventilation has been successfully described in some patients with cystinosis and has been associated with improved survival in other disease states [21, 54, 55].

Further strategies to support patients with cystinosis and pulmonary dysfunction include avoiding smoking and/or creating a smoking cessation plan; receiving the COVID-19, influenza, pneumococcal, and other vaccines, as appropriate; maintaining a healthy weight; aggressively treating infections; and optimizing the control of underlying respiratory conditions, such as asthma [21, 26, 52].

Summary and conclusions

Although the kidneys are the first and most seriously affected organ in cystinosis, over time the disease eventually progresses to a phenotype dominated by extrarenal sequelae. Myopathy, a common complication in cystinosis, has significant implications, potentially leading to weakness of the distal and proximal muscles and the muscles involved in eating, swallowing, and breathing. This review aimed to summarize the current understanding of myopathy in cystinosis and provide best practices to support monitoring, assessment, management/mitigation strategies, and specialist referrals.

Routine monitoring for muscle involvement should ideally begin in the pediatric care setting and continue into adulthood. Monitoring for myopathy in the primary cystinosis practice is largely reliant on clinical history and patient-reported symptoms, which can be challenging, as patients may develop compensations for impairments and may be unable to recognize the full extent of their disease. Clinicians can tailor questions to focus on ADLs and functional changes to assess the development or progression of muscle involvement and ensure appropriate timing of referral to additional specialists.

Similar to other extrarenal complications of cystinosis, specialist involvement is warranted for further assessment and management if muscular dysfunction is suspected. Depending on the extent of disease severity, it may be appropriate to refer patients to physical, occupational, speech, or respiratory therapists; additional specialists may include neurologists, pulmonologists, gastroenterologists, otolaryngologists, physiatrists, orthopedists, dentists, and dietitians. If available, referral to comprehensive care clinics experienced in neuromuscular disorders may be an effective way to streamline care across multiple specialists and lessen the burden on patients with cystinosis.

Cystine toxicity is thought to contribute to the development of myopathy in patients with cystinosis, underscoring the recommendation for early and continuous cysteamine therapy. For patients who are untreated or undertreated, cysteamine may still be beneficial. Aside from cysteamine, current myopathy management is largely supportive and based on patient symptomatology.

There are many gaps that remain in our understanding of myopathy in cystinosis. Further studies are needed to clarify the pathophysiology and phenotypic variability seen in patients with myopathy. Additional research on appropriate management strategies for cystinosis myopathy is warranted, including more robust studies of the potential benefit of respiratory training, various exercise regimens, and approaches to supplementation. Investigational therapies for cystinosis, such as gene therapy, aim to prevent multiorgan damage and negate the need for lifelong treatment. Until new therapies become available in cystinosis, clinicians should make every effort to monitor for and provide supportive care for myopathy-related sequelae of the disease.

Supplementary Information

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Additional file 1. Videofluoroscopic swallowing study results of a patient with cystinosis.

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Declarations

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