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Systematic Review/Meta-Analysis

Diffuse idiopathic skeletal hyperostosis of the cervical spine causing dysphagia and airway obstruction: an updated systematic review

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Abstract

BACKGROUND AND CONTEXT: Diffuse idiopathic skeletal hyperostosis (DISH) is characterized by growing ossifications of spinal entheses and tendons, which may cause trachea and esophagus compression when located anteriorly in the cervical spine.

PURPOSE: Our previous systematic review on the epidemiological and clinical knowledge of dysphagia and airway obstruction caused by cervical DISH was updated, with a focus on (surgical) treatment and outcomes.

STUDY DESIGN: A systematic review of the literature was performed.

METHODS: Publications in Medline and EMBASE from July 2010 to June 2021 were searched. Two investigators performed data extraction and study specific quality assessment.

RESULTS: A total of 138 articles (112 case reports and 26 case series) were included, describing 419 patients with dysphagia and/or airway obstruction. The mean age of the patient group was 67.3 years (range: 35–91 years), and 85.4% was male. An evident increase of published cases was observed within the last decade. Surgical treatment was chosen for 66% of patients with the anterolateral approach most commonly used. The total complication rate after surgery was 22.1%, with 12.7% occurring within 1 month after intervention. Improvement of dysphagia was observed in 95.5% of operated patients. After a mean follow-up of 3.7 years (range: 0.4–9.0 years), dysphagia recurred in 12 surgically treated patients (4%), of which five patients had osteophyte regrowth.

CONCLUSIONS: The number of published cases of dysphagia in patients with DISH has doubled in the last decade compared to our previous review. Yet, randomized studies or guidelines on the treatment or prevention on recurrence are lacking. Surgical treatment is effective and has low (major) complication rates. Common trends established across the cases in our study may help improve our understanding and management of dysphagia and airway obstruction in cervical DISH. © 2022 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/)

Keywords:

Diffuse idiopathic skeletal hyperostosis; DISH; Dysphagia; Airway obstruction; Forestier's disease, Osteophytes; OALL; Systematic review

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Diffuse idiopathic skeletal hyperostosis (DISH) is a systemic condition characterized by the formation of new bone at ligamentous and tendinous insertions of the spine. The most common manifestation of DISH is near the anterolateral aspect of the thoracic spine, but DISH can also be present in the peripheral skeleton [1,2]. DISH is more frequently seen in males and is related to older age, with a prevalence up to 42% in patients over the age of 65 [3]. DISH is most commonly diagnosed using the Resnick and Niwayama criteria which requires the presence of flowing calcification and/or ossification along the anterolateral aspect of at least four contiguous vertebral bodies; (relative) preservation of intervertebral disc height; and absence of apophyseal joint ankylosis and sacroiliac joint changes [4]. The exact pathophysiology of DISH remains unclear, but various genetic, metabolic and inflammatory factors have been hypothesized to be involved as DISH is associated with obesity, type 2 diabetes, and the metabolic syndrome [5]. Patients with DISH are also more at risk for spinal fractures and stroke [1,6]. Reported symptoms related to DISH are usually limited to back pain, morning stiffness, or a reduced range of motion [7].

Previously, our group performed a systematic review on case reports and case series describing dysphagia and airway obstruction in relation to cervical DISH. This index study showed a steadily increase in the prevalence of reported DISH-related dysphagia and airway obstruction between 1980 and 2009 [8]. As the global burden of obesity, diabetes, and the metabolic syndrome are projected to increase in the coming years, a simultaneous increase in prevalence of (cervical) DISH should be expected. We hypothesize that since our previous review published in 2011, the number of published cases with dysphagia and airway obstruction due to DISH has risen further. Therefore, in the current study we aimed to provide an update of our previous systematic review regarding the number of published cases, patient characteristics, treatment, and outcomes of dysphagia and airway obstruction due to DISH. In addition to updating the epidemiological and clinical knowledge, we performed supplementary analyses such as a comprehensive quality assessment of study domains, in regards to the selection, ascertainment, causality, and reporting of each study.

Materials and methods

Data sources and searches

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and has been registered in PROSPERO (CRD42021231126) [9]. We performed a systematic literature search of Medline and Embase for articles describing cases with the unequivocal presence of DISH with unequivocal dysphagia and/or airway obstruction. The search was queried for articles published between July 2010 and June 2021, as the previous review included articles up until June 2010. An updated search syntax was applied using a combination of the terms "diffuse idiopathic skeletal hyperostosis" AND ("dysphagia" OR "airway obstruction"), and relevant synonyms. The full search can be found in Appendix A. No language restrictions were applied and authors were not contacted in case of missing data. During full text review, cross-referencing was used to identify additional articles not included in the initial screening.

Study selection

Two investigators (N.I.H. and J.S.K.) independently screened the title and abstracts, and resolved conflicts by reaching consensus. Screening consisted of two rounds to ensure only definite cases of DISH were included. Using the same inclusion criteria as the previous review [8], the first round of review included articles when all of the following four criteria were met: unequivocal presence of dysphagia and/or airway obstruction; potential presence of DISH or established diagnosis of DISH; absence of other pathological conditions of the cervical spine and/or pharyngeal/laryngeal structures (all cases with a history of cervical trauma and/or surgery were excluded); and an adequate clinical and/or radiological description of each individual case. The formal diagnosis of DISH (or one of its synonyms) as established by the original authors was accepted. Using the Resnick criteria [4], potential cases of DISH were critically appraised for unequivocal DISH by the present authors, provided that lateral radiographs, sagittal computed tomography images, or sagittal magnetic resonance images of sufficient image quality were available.

Data extraction and quality assessment

Data extraction and quality assessment were performed by one investigator (N.I.H.). A second reviewer (J.S.K) checked the data extracted from the original articles, with conflicts resolved by consensus. To assess the quality of each study, we utilized the framework for methodological quality and synthesis of case series and case reports as described by Murad et al [10]., which assesses the study domains selection, ascertainment, causality, and reporting of each study. We defined case reports as articles describing one or two individuals with DISH with concurrent dysphagia and/or airway obstruction, and case series as articles describing three or more individuals.

Dysphagia was classified in four categories: "Mild": when patients were able to swallow solid food; "Moderate": when patients were only able to swallow liquids; "Severe": if they were not able to ingest fluids at all; and "Not specified": if the degree of dysphagia was not described in sufficient detail [11]. Airway obstruction was categorized as "Mild": if patients suffered from occasional stridor or occasional aspiration or dyspnea with heavy exercise (not related to cardiopulmonary or other systemic conditions as concluded from the original texts); "Moderate": when patients experienced permanent non-life-threatening stridor or frequent aspiration or dyspnea with light exercise; "Severe": if patients had permanent life-threatening stridor, frequent aspiration with life threatening complications or dyspnea in rest; and "Not specified": if the degree of airway obstruction was not adequately described. Extracted data parameters have been described in detail previously [8], and included age, sex, severity and duration of dysphagia and/or airway obstruction, patient comorbidities and symptoms related to DISH, treatment, patient follow-up, and complications/adverse events. Treatment was divided into operative and non-operative treatment. Postoperative complications (adverse events within 1 month), long term complications (adverse events after 1 month), and secondary procedures were recorded if available until the latest follow-up. The improvement of dysphagia or airway obstruction as established by the original authors was also assessed using the previous described classification.

Statistics

Categorical data were displayed using frequencies and percentages, and numerical data using mean and standard deviation (SD). To compare differences between the operative and non-operative group, independent sample t tests and chi-square tests were used to calculate the differences regarding, age, sex, severity and duration of symptoms, and the number of affected and symptomatic vertebral levels. A p-value <.05 was considered significant. Data analysis was performed using R, version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Study identification and characteristics

After discarding duplicates, 366 articles were screened on title and abstract, of which 256 articles were assessed using full text screening. The total number of included studies was 138 (including five articles identified after cross referencing), encompassing 112 case reports and 26 case series (Fig. 1), describing a total of 419 patients with dysphagia and/or airway obstruction [12–148]. A comprehensive description of quality assessment of study domains for each article is listed in Appendix B.

Location demographics of included papers were from European (n=55, 203 cases), Asian (n=50, 108 cases), North American (n=20, 54 cases), African (n=7, 47 cases), South American (n=5, six cases), and Australian (n=1, one case) institutions Fig. 2 displays the number of reported cases by country, in both the previous (Fig. 2A) and current (Fig. 2B) review. The number of cases and publications per year is shown in Fig. 3. A steady increase in published cases was observed between 2010 to 2020 with triple the number of cases published in 2016 to 2020 compared with 2010 to 2015 (298 vs. 96). Cases and publications from 1980 to the present are shown in Fig. 4, which shows both an increase in publications and published cases.

Patient demographics

Of the 419 included patients with DISH, age was described for 386 patients, with the mean age of the total group being 67.3 years (SD: 8.6, range: 35–91).

Stratified by age group, there were nine patients (3.1%) between 35 to 45 years; 21 cases (7.2%) between 46 to 55 years; 79 cases (27.1%) between 56 to 65 years; 92 cases (31.6%) between 66 to 75 years; 53 cases (18.2%) between 76 to 85 years; and four individuals (1%) older than 85 years. For 128 patients included in case series only the mean age (+SD) of the population was described. Sex was specified for 386 patients, comprising 330 males and 56 females suggesting a male-to-female ratio of 5.9 to 1. The mean age was 67.6 years for men and 65.6 years for women, which was not significantly different (p=.14).

Dysphagia was present in 414 patients: 5 (1%) patients had no dysphagia, 99 patients (23.4%) had mild dysphagia, 57 (13.6%) had moderate dysphagia, 8 (1.9%) experienced severe dysphagia, and 250 patients (59.8%) had dysphagia in which the severity was not sufficiently described.

Airway obstruction was present in 60 patients comprising severe (n=8), moderate (n=3), mild (n=3), and insufficiently described (n=46). Fifty-five patients suffered from both dysphagia and airway obstruction. The duration of dysphagia at presentation was described for 156 patients, and ranged from 3 to 5048 days (mean=663, SD=786.5 days). The duration of airway obstruction at presentation was described for 15 patients ranging from 1 day to 2920 days (mean=390, SD=765.9 days).

Imaging modalities used to diagnose DISH included plain cervical radiographs (n=278, 66.3%), computed tomography (n=238, 56.8%), barium swallow radiographs (n=238, 56.8%), laryngoscopy (n=185, 44.2%), and magnetic resonance imaging (n=109, 26%).

For 268 cases the distribution of vertebrae affected by DISH was described comprising C1 (n= 5), C2 (n=107), C3 (n=211), C4 (n=257), C5 (n=249), C6 (n=203), and C7 (n=136) (Fig. 5A). The number of cervical vertebrae affected by DISH was adequately described in 269 cases: A total of 41 individuals had two levels involved, 40 had three levels involved, 61 had four levels involved, 65 had five levels involved, 60 had six levels involved, and two individuals had all seven cervical levels involved. The average number of affected vertebrae was 4.3. The levels held mainly responsible for symptoms of dysphagia and/or airway obstruction (136 levels reported in 120 cases) were C1 (n=1), C2 (n=12) C3 (n=41); C4 (n=51), C5 (n=19), and C6 (n=12) (Fig. 5B). Additional observations on imaging included ossification of the posterior longitudinal ligament in 49 subjects out of 419 (11.7%).

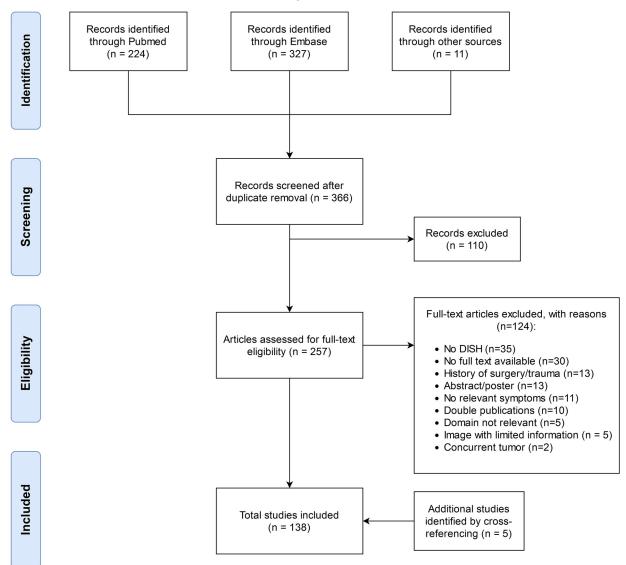


Fig. 1. PRISMA flowchart of study selection.

Related symptoms associated with DISH were reported in 215 patients and were most frequently weight loss (n=62), neck pain (n=62), dysphonia (n=55), and a limited cervical range of motion (n=38). A more detailed description is listed in Table 1.

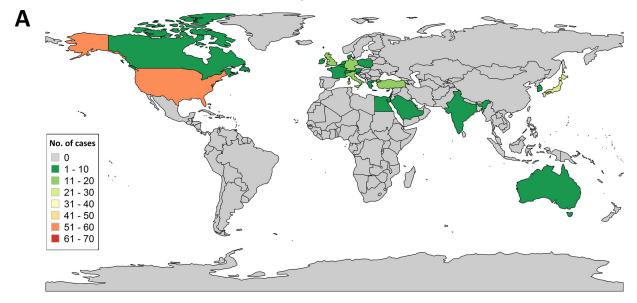
Comorbidities are listed in Table 2 and were reported in 100 patients, with diabetes (n=57), hypertension (n=55), and obesity (n=21) most frequently reported.

Treatment

In 70 of the 419 cases (16.7%) the treatment was not adequately described, in some reports patients were referred for treatment to a different institution. An acute intervention, either emergency intubation or tracheostomy, was performed in 11 of the 60 patients (18.3%) with airway obstruction.

Conservative treatment was chosen for 90 patients and consisted of (in various combinations) dietary measures (n=72), nonsteroidal anti-inflammatory drugs (n=64), corticosteroids (n=54), antireflux drugs (n=53), muscle relaxants (n=53), postural changes (n=26), rehabilitation therapy (n=6), antibiotics (n=2), gastrotomy (n=2), bisphosphonates (n=1) and gastric prokinetics (n=1).

Elective surgical treatment was selected for 276 patients (66%), while eight patients refused surgical treatment. Operative removal of anteriorly located osteophytes were performed with the following surgical techniques/ approaches: anterolateral approach (n=263), unspecified approach (n=8), transoral approach (n=5). This was sometimes combined with additional surgical procedures, including spinal fusion (n=38), cricopharyngeal myotomy (n=9), decompression (n=3), partial discectomy (n=2), partial vertebrectomy (n=2), corpectomy (n=2), and arthrodesis (n=2).



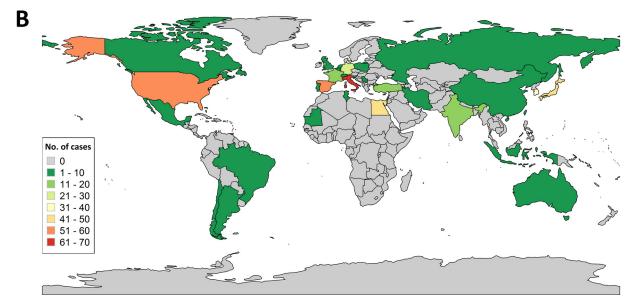


Fig. 2. (A) The total number of published cases of dysphagia and/or airway obstruction by country between 1980 and 2009. (B) The total number of published cases of dysphagia and/or airway obstruction by country from 2010 to the present. Maps were created using open-source data from the R package "rworldmap" (https://cran.r-project.org/package=rworldmap).

A tracheostomy during surgery was performed in 22 patients (8%). Postoperative radiotherapy following surgery was performed in seven patients, and four patients received prophylactic indomethacin to prevent recurrent bone growth.

We found no significant differences between patients treated operatively or nonoperatively regarding patient age and gender, duration of symptoms, or number of affected and symptomatic vertebrae.

Early post-surgical complications

Two patients died before they could undergo surgery due to cardiorespiratory arrest (n=2). For 35 subjects

(12.7%) complications were reported within one month of treatment, shown in Table 3. Most common complications following surgery included additional dysphagia (n=7), dysphonia (n=6), dyspnea (n=3), requirement for endotracheal intubation (n=1) and tracheostomy (n=1), hemorrhage (n=3), and hematoma (n=3). The most severe complication occurring within 1 month was cardiopulmonary arrest leading to permanent brain damage (n=1).

Long-term follow-up and late complications

The follow-up duration was reported for 286 cases with an average of 828 days (median: 730 days, range: 2–4015),

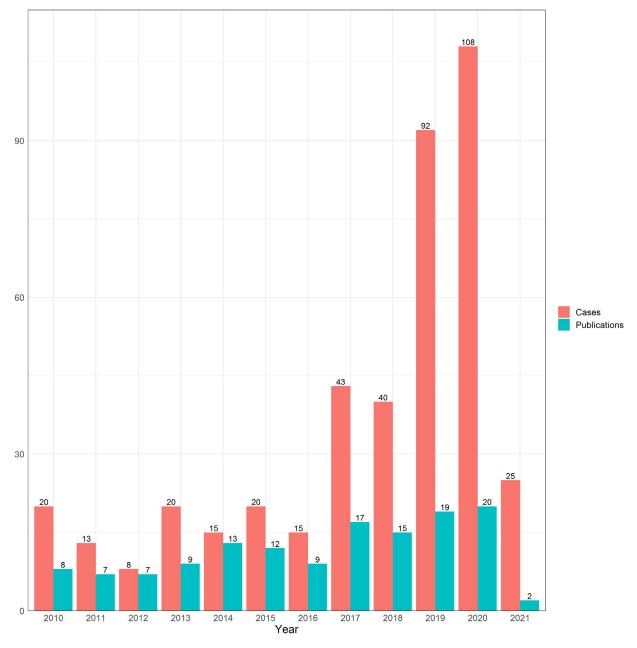


Fig. 3. The number of cases and publications sorted by year of publication in the last decade.

which included 246 surgically treated patients. Complications after one month were reported for 26 patients (9.4%) (Table 3) and most frequently consisted of recurrence of dysphagia (n=12) following regrowth of cervical osteophytes (n=5) after a mean follow-up of 3.7 years (range: 0.4–9 years), which required secondary resection of the anterior osteophytes in three patients. The most severe complication was airway swelling due to DISH resulting in cardiopulmonary arrest and death (n=2). Definite improvement was reported for 247 patients, of which 236 (95.5%) had improvement of dysphagia at last follow-up.

Discussion

In this updated systematic review, 419 patients with dysphagia and/or airway obstruction as a result of cervical DISH were identified in the literature since July 2010. In the last decade, the number of published cases was more than double the amount identified in our first review, which encompassed all patients within a 30-year time-frame from 1980 to 2009 [8]. This increase in reports was evident as the years 2015 to 2020 had triple the number cases published compared with 2010 to 2015. Even though the number of case series were similar between reviews (26 vs. 23),

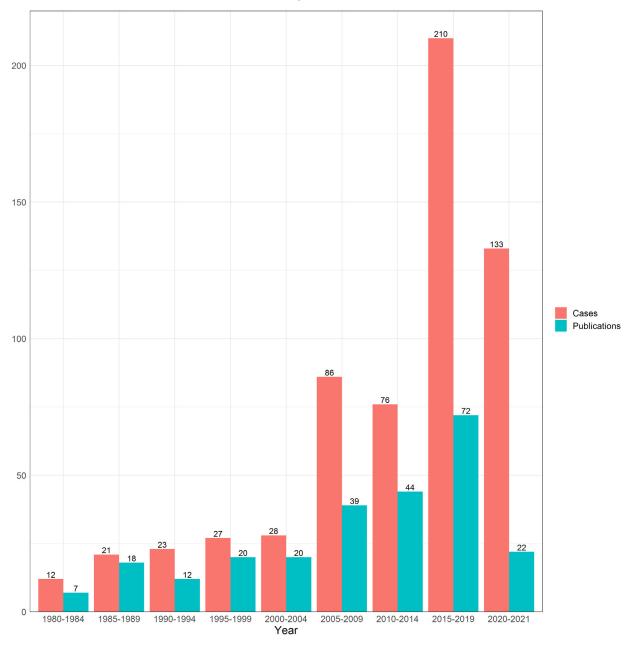


Fig. 4. The number of cases and publications from 1980 to the present.

larger patient samples with symptomatic cervical DISH were published in the last decade. This may support the notion that more authors have increased awareness and interest in DISH and its associated complications and potential for treatment. We cannot exclude, however, that this increase may also be partly due to a rise in the number of publications over time. For airway obstruction, the number of patients reported has remained stable. In line with our first review, most published cases were from European institutions. We observed large increases in the number of published cases in Europe, Asia, and Africa, while a smaller number of published cases was seen in North America when comparing location demographics.

Furthermore, the gender distribution and age of patients affected by cervical DISH has remained unchanged, and we showed again that dysphagia may occur at a young age (below 40 years), supporting our previous findings.

It is estimated that the incidence of cervical dysphagia due to DISH is around 7:100.000 [125]. In contrast to DISH in the thoracic spine, bone in cervical DISH is deposited mostly in the midline resulting in direct mechanical compression of the esophagus and airway [149,150]. This chronic obstruction may result in local inflammatory reactions, causing fibrosis and adhesions around the esophagus and soft tissues [77].

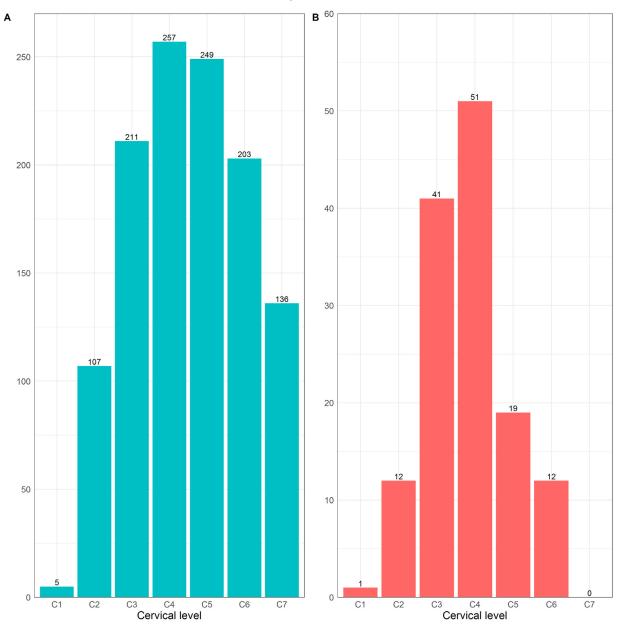


Fig. 5. (A) The distribution of affected cervical DISH levels. (B) Reported levels responsible for symptoms of dysphagia and/or airway obstruction.

Conservative treatment is usually the first choice of treatment in symptomatic cervical DISH, usually consisting of dietary measures, physical and swallowing therapy, with or without the addition of pain medication, corticosteroids, or antireflux drugs and muscle relaxants, none of which have been proven effective.

When conservative symptomatic interventions are insufficiently effective or when there is a progression of clinical symptoms, surgery is usually indicated.

Surgical treatment was chosen for 66% of patients in our review, with the anterolateral approach most commonly used. Dysphagia improved in 95.5% of patients following surgical treatment. Earlier surgical intervention has been positively associated with a complete resolvement of

dysphagia in DISH [147]. Therefore, based on their experience, Lofrese et al [147]. recommended surgical treatment even in mild cases of dysphagia based on expert opinion.

While surgical treatment predominantly consisted of osteophytectomy alone in our sample, few case series have combined osteophytectomy with other surgical procedures.

Some authors postulated that upper esophageal sphincter dysfunction may contribute to dysphagia, in which cricopharyngeal myotomy may be effective [126]. In a series of nine patients undergoing osteophytectomy and cricopharyngeal myotomy, dysphagia resolved immediately and the complication rate was low, though dysphagia recurred in two patients during long term follow-up. Van der Hoeh et al [66]. recommend resection and intervertebral fusion Table 1

Reported symptoms related to DISH in 215 patients

Symptom	N (%)	
Weight loss	62 (29)	
Neck pain	62 (29)	
Dysphonia	55 (26)	
Limited range of motion	38 (18)	
Sleep apnea/snoring	20 (9)	
Aspiration	20 (9)	
Myelopathy	20 (9)	
Cough	17 (8)	
Odynophagia	13 (6)	
Respiratory insufficiency	8 (4)	
Aspiration pneumonia	8 (4)	
Difficult intubation	7 (3)	
Instability and dizziness	6 (3)	
Choking	3 (1)	
Radiculopathy	2 (1)	
Pharynx perforation	1 (0.5)	
Nausea and vomiting	1 (0.5	

Table 2

Reported comorbidities in 100 patients

Comorbidity	N, %
Diabetes mellitus	57 (57)
Hypertension	55 (55)
Obesity	21 (21)
Coronary artery disease	12 (12)
Dyslipedemia	11 (11)
Atrium fibrillation	8 (8)
Ankylosing spondilitis	3 (3)
Metabolic syndrome	2 (2)

with PEEK cages for stability and prevention of regrowth. In their series of six patients, dysphagia resolved and no regrowth occurred at a mean follow-up of 24 months. It is unclear whether anterior screw and plate fixation is superior or inferior to osteophytectomy alone. Some authors suggest that plate fixation may lead to further compression of the

Table 3

Reported complications within and after 1 month

Hypoglossal nerve palsy (n=1)

esophagus	[151], wherea	s others	hypothesize	fixation	may
prevent reg	rowth of the or	steophyte	es [120].		

As studies are predominantly case reports and retrospective case series, drawing evidence-based conclusions on the efficacy and superiority of (surgical) treatment for symptomatic cervical DISH is difficult.

Future efforts should be aimed at conducting a Delphi method of consensus for symptomatic cervical DISH in order to integrate international and interdisciplinary perspectives from academics, orthopedic surgeons, and otolaryngologists with relevant expertise, before performing a randomized controlled trial.

Otolaryngologic manifestations of DISH have also been reported in another review [152]. Compared to our study, the authors found less cases within the same time-frame, leading to an underestimation of the published cases. Moreover, the authors reported no (major) complications and no recurrence of osteophytes or symptoms. We observed a total complication rate of 22.4% following surgery. In our results, although rare, cervical DISH led to cardiopulmonary arrest with death as a result of airway swelling, both prior to- and after operative treatment [56,83,124]. Our previous review identified 12 patients with osteophyte recurrence. Currently, we reported 12 patients with recurrent dysphagia, including regrowth of osteophytes in five patients, remarkably after a period of 9 years following surgery [99].

Few authors recommend postoperative radiotherapy with or without indometacin for patients over the age of 55 to prevent further surgical intervention [51,112], though no consensus exists on the prophylactic management of recurrence. Given the extended period needed for osteophyte regrowth, long term follow-up of these patients is warranted.

Inherent limitations of reviews based on case reports are incomplete validity assessments and the inability to appraise publication bias. Furthermore, a portion of included studies had missing population and outcome data,

Complications within 1 mo (n=35)	Complications after 1 mo (n=26)		
Dysphonia (n=10)	Recurrence of dysphagia (n=12), with osteophyte regrowth (n=5)		
Additional dysphagia (n=7)	Aspiration symptoms (n=2)		
Dyspnea (n=3) with intubation (n=1) and tracheostomy (n=1)	Death due to DISH with cardiopulmonary arrest (n=2)		
Hematoma (n=3)	Residual neck pain and bilateral hand numbness (n=1)		
Hemorrhage (n=3)	Hematoma and infection of pharyngeal mucosa (n=1)		
Laryngeal edema requiring emergency tracheotomy (n=1)	Laryngeal edema (n=1)		
Cardiopulmonary arrest leading to brain damage (n=1)	Stroke (n=1)		
Transient recurrent nerve paralysis (n=1)	Deep infection (n=1)		
Right sided weakness (n=1)			
Aphagia requiring tracheostomy (n=1)			
Aphagia requiring feeding tube (n=1)			
Stroke (n=1)			
Esophageal tear (n=1)			

meaning selective reporting bias could not be fully ascertained (Appendix B). We suggest that future studies reporting dysphagia in DISH should adhere to validated severity scales [11]. Nonetheless, we have reviewed the largest collection of cases of dysphagia and airway obstruction in DISH in this updated review. Other strengths of our study include the comprehensive and updated expert literature search without language restriction, assessment of study-specific methodological quality, and attempts to exclude bias wherever possible with our strict in- and exclusion criteria.

Conclusion

In this updated systematic review, the number of published cases of dysphagia in patients with DISH has doubled in the last decade compared to our previous review. Complication rates following surgery were up to 22%, with symptoms of recurrent dysphagia and osteophyte regrowth occurring in some instances even at long term follow-up. Randomized studies or guidelines on the treatment of cervical DISH are lacking. Common trends established across the cases in our study may help improve our understanding and management of dysphagia and airway obstruction in cervical DISH.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations of competing interests

The authors of the manuscript have no competing interests to declare.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j. spinee.2022.03.002.

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