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Review

Pathophysiology of cachexia and characteristics of dysphagia in chronic diseases

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ABSTRACT

Cachexia is a condition characterized by skeletal muscle loss, weight loss, and anorexia. It is a complication of many diseases, not only cancer, and is characterized by chronic systemic inflammation. Cachexia and sarcopenia share common factors. The various symptoms observed in cachexia may be caused by multiple factors and inflammatory cytokines secreted by a tumor. Essentially, sarcopenia develops with aging, but it can occur at younger ages in the presence of cachexia, malnutrition, and disuse syndrome. In a recent study, dysphagia was found to be closely associated with malnutrition and sarcopenia. Factors specific to chronic diseases may influence the clinical outcome of dysphagia. Elderly people frequently exhibit dysphagia, but no research has been reported on whether cachexia is directly linked with dysphagia. Dysphagia is an important clinical problem, leading to aspiration pneumonia, suffocation, dehydration, malnutrition, and death. In addition to treating the patient, the degree of dysphagia needs to be accurately assessed. This review focuses on the pathogenesis of cachexia and the prevalence of dysphagia-related diseases, methods of assessment, and their impact on clinical outcomes.

Introduction

Cachexia is a complex metabolic disease characterized by progressive skeletal muscle loss (sometimes accompanied by fat loss). The incidence of cachexia is about 11% of patients worldwide,[1] about 50% in all patients with cancer, and is reported to be the cause of about 30% of deaths.[1,2] The incidence of cachexia in patients with cancer is very high, but it varies depending on the type of tumor. However, the mechanisms linked with cachexia are not fully characterized. Cachexia has been linked not only with cancer but also with chronic obstructive pulmonary disease (COPD), chronic heart failure (CHF), liver failure, and acquired immune deficiency syndrome. Various symptoms observed in cachexia may be due to a variety of factors and inflammatory cytokines secreted by the tumor. Cachexia and sarcopenia share common factors. The systemic inflammation that occurs in cachexia causes marked muscle catabolism,[3,4] giving rise to sarcopenia. In patients with cancer, cachexia is a prognostic factor, predisposing to postoperative complications, reducing resistance to chemotherapy and radiotherapy, and decreasing the effectiveness of anticancer therapy.[5] In COPD, repeated exacerbations increase the complication rate of cachexia as the primary disease progresses.[6] Cardiac cachexia is an involuntary and progressive loss of

weight.[7] With the progression of cachexia symptoms, there is a rapid decline in nutritional status and physical function. Cachexia should be viewed as a multifactorial nutritional and metabolic disorder that requires early intervention.[8]

Recent studies have shown that dysphagia is closely associated with hyponutrition and sarcopenia.[9] Furthermore, the development of dysphagia during hospitalization is negatively correlated with the 1-year survival and functional recovery in patients with heart failure.[10] Factors specific to chronic diseases may influence the clinical outcome of dysphagia. On the other hand, dysphagia may cause sarcopenia via undernutrition, but a direct link has not been elucidated. Furthermore, it has not been verified whether dysphagia is directly caused by cachexia. Unlike head, stroke, and neck diseases, for which dysphagia is well-documented, there are few reports on dysphagia in patients with COPD and CHF. For more information on the association between dysphagia and cancer cachexia, there is only one report of a patient with cervical/head cancer who presented with dysphagia and weight loss at the start of treatment.[11] Some assessment methods may underestimate dysphagia because there is a marked variation in the way dysphagia is assessed in different studies. Dysphagia is a serious problem that can lead to poor nutrition, aspiration pneumonia, choking, dehydration, and

death; therefore, the degree of dysphagia must be accurately assessed and treated. This review focuses on the pathogenesis of cachexia and dysphagia in significant diseases, its prevalence, prognosis, interventions, and assessment methods. It also discusses the evidence to date and future research directions in this area.

Cachexia

Definition of cachexia

Cachexia is a complex metabolic disease characterized by progressive skeletal muscle loss (sometimes accompanied by fat loss) that leads to a variety of functional disorders and is difficult to ameliorate with conventional nutritional therapy.[12] The incidence of cachexia in patients with cancer is very high but varies depending on the type of tumor. Patients with gastric and pancreatic cancers have an incidence of more than 80%, while patients with colon, prostate, and lung colon cancers have an incidence of about 50%, and patients with breast and lung cancers have an incidence of about 40%.[13] However, the underlying mechanism that induces cachexia has not been comprehensively proven. Cachexia is associated with cancer, COPD, CHF, liver failure, inflammatory conditions, and acquired immune deficiency syndrome. In 2011, a definition of cancer cachexia was published, stating that it is "a complex condition characterized by marked muscle tissue loss that is difficult to correct with conventional nutritional support and causes progressive functional impairment with or without the loss of adipose tissue.[8] This definition, along with the stage classification, is used worldwide when considering cancer cachexia. The mechanism of cancer cachexia progression has not yet been established, but three stages are considered: pre-cachexia, cachexia, and refractory cachexia. The diagnostic criteria for cachexia are weight loss of 5% or more within 6 months or weight loss of 2% or more with sarcopenia.[12]

Condition of cachexia

Cachexia is a condition characterized by skeletal muscle, weight loss, and anorexia. It is a complication of many diseases, not only cancer, and is caused by systemic chronic inflammation. In cachexia, catabolism is increased by metabolic abnormalities and anorexia, resulting in malnutrition that is resistant to treatment.[13,14] Starvation leads to a loss of adipose tissue, but cachexia causes the early loss of skeletal muscle.

Substances that play an important role in cachexia are proinflammatory cytokines. Metabolic abnormalities and anorexia are linked with the activation of inflammatory cytokines interleukin-1 (IL-1), tumor necrosis-factor-α (TNF-α), IL-6, etc.), which play a central role in the pathogenesis of cachexia. The activation of inflammatory cytokines not only affects these abnormalities but also causes peristaltic dysfunction and edema of the gastrointestinal tract, exacerbating anorexia, and reducing digestive and absorptive functions. It is considered that inflammatory cytokines impair the secretion of corticosteroid-releasing hormone and appetite-stimulating neuropeptide Y, which, in turn, leads to the progression of anorexia.[15] Anorexia has been reported to be present in 15%–40% of patients with cancer and 80% of patients with end-stage cancer. In addition, digestive and mechanical factors have been identified.[16] Tumors and chemotherapy cause nausea, dysphagia, dysfunction, mucositis, and malabsorption, resulting in decreased body weight and food intake. The consensus definition of cachexia is a decrease in oral intake due to anorexia, adverse events, or gastrointestinal transit disruption from cancer treatment (eg. radiation therapy, chemotherapy, and surgery).[17] Decreased oral intake due to food intolerance and weight loss in cachexia can affect dysphagia and nutritional disorders, which can have a significant impact on the prognosis.

Definition of dysphagia

Putting water or food into the mouth from outside and sending it through the pharynx and esophagus to the stomach is called swallowing.

Dysphagia is caused by an abnormality in one or more of the following processes. Oropharyngeal dysphagia (OD) is classified as a digestive condition by the International Classification of Diseases, ICD-10 and is the international Classification of Functioning, Disability, and Health code B5105 of the World Health Organization.[18,19] Experts of the Dysphagia Working Group recently recognized dysphagia as a 'geriatric syndrome', defined by the difficulty of effectively and safely moving the alimentary bolus from the mouth to the esophagus.[20,21]

The swallowing movement is divided into four stages: the oral preparation stage, oropharyngeal stage, pharyngeal stage, and esophageal stage. The first two stages correspond to the formation and feeding of the pharynx and food mass into the pharynx.[20] The pharyngeal phase is the swallowing reflex phase, which requires a precise coordination of swallowing and breathing to protect the airway. At the esophageal level, peristalsis transports the food mass to the stomach. More than 25 muscles and seven cranial nerves are involved in swallowing, and nerve and muscle defects can affect swallowing. It is necessary to understand swallowing as a series of movements and evaluate each stage (Fig. 1).

Pathophysiology of dysphagia

Dysphagia can lead to serious consequences such as poor nutrition, dehydration, choking, aspiration pneumonia, and death. OD increases with age,[22] but the reported prevalence estimates across studies are highly variable. The prevalence of OD has been calculated in older persons across different settings, with rates between 30% and 40% in independently living older people,[23] 44% in those admitted to geriatric acute care,[24] and 60% in institutionalized older people.[25] The increased risk of dysphagia can be attributed to multiple factors, including age-related changes in head and neck anatomy, and changes in neural and physiologic mechanisms that control swallowing and increasing disease. Age-related changes in the mouth, pharynx, larynx, and esophagus together with age-related neurological diseases predispose older people to dysphagia.[26] Anatomical changes include a high proportion of head and neck cancers. Dysphagia associated with head and neck cancer can be categorized as (1) tumor-induced, (2) radiotherapy-induced, and (3) surgery-induced. Table 1 shows the characteristics of radiotherapy-induced and surgical dysphagia and potential interventions. Physiological changes are often associated with cerebrovascular disease and central nervous system disorders such as Parkinson's. In cerebrovascular disease, pseudobulbar palsy due to multiple brain lesions and bulbar palsy patients due to brainstem lesions are representative. Table 2 shows the characteristics of dysphagia in pseudobulbar palsy and bulbar palsy and the potential for intervention. Dysphagia in patients with Parkinson's disease is a significant prognostic determinant. The entire swallowing motor process is impaired, from the antecedent to the esophageal phase. Table 3 shows the features of dysphagia in Parkinson's disease patients and the potential for intervention. OD is frequently observed in those with cerebrovascular disease, head and neck cancer, and progressive neurological diseases (dementia, ALS, Parkinson's disease, etc.). The incidence of OD has been reported to be 54% in stroke patients,[20] about 50% in head and neck cancer patients,[27] and more than 80% in dementia patients.[20] In addition, dysphagia is associated with functional decline,[28] a prevalent risk factor for malnutrition,[29] and is very common in community-dwelling elderly.[30] For example, it has been reported that 6.1%–62% of patients with stroke,[31] 67% of those with head and neck cancer,[32] and up to 100% of patients with ALS,[33,34] the leading causes of dysphagia, are at risk of hypo- or undernutrition. Stroke patients with dysphagia have a 2.4-fold higher risk of hyponutrition compared with non-dysphagic patients.[35] Physical function and dysphagia are closely associated with hyponutrition. Aging is the main cause of sarcopenia, but sarcopenia can also occur at younger ages when there is a combination of cachexia, malnutrition, and disuse syndrome. In a recent study, dysphagia was shown to be closely associated with hyponutrition and sarcopenia.[9] Furthermore, dysphagia during hospitalization has been suggested to be negatively

| Oral preparatory stage | Oropharyngeal stage | Pharyngeal stage | Esophageal stage |
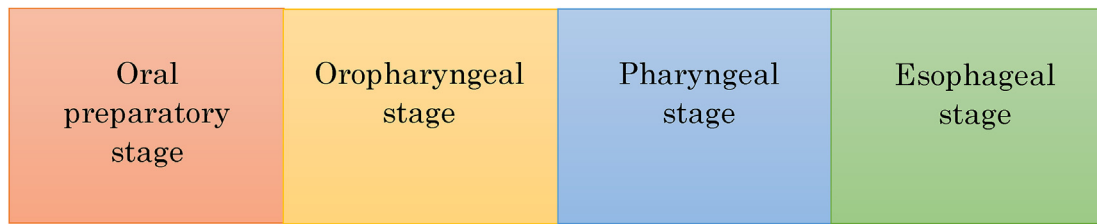
Fig. 1. Four – stage model of the stages of dysphagia. The process of swallowing can be divided into four consecutive stages: (1) oral preparatory stage, (2) oropharyngeal stage, (3) pharyngeal stage, (4) esophageal stage.

Table 1
Characteristics of head and neck cancer-related dysphagia and potential interventions.

	Characteristics	Possible interventions
Radiotherapy-induced dysphagia	(1) Effect of concurrent chemotherapy • Severe mucositis (2) Acute phase • Salivary secretion disorder • Taste disorder • Mucositis • Pain • Laryngeal hypoesthesia (3) Chronic phase • Prolonged dysphagia (4) Late stage • Sensory and sensory disturbance of mucous membranes • Muscle weakness due to atrophy/fibrosis of swallowing-related muscle groups	• Continuation of oral intake • Adjustment of meal form • Selection of compensatory feeding methods • Oral hygiene • Nutritional management • Prevention of aspiration pneumonia
Dysphagia after surgery	• Glottal atresia • Impaired laryngeal elevation • Impaired lower airway defense • Deformity of the food mass passage	• Breath-hold swallowing technique • Shaker exercise • Mendelsohn method • Pre-operative rehabilitation

Table 2
Characteristics of dysphagia and potential interventions in pseudobulbar and sphincter palsy.

	Characteristics	Possible interventions
Pseudobulbar palsy	(1) Aphasia (2) Higher brain dysfunction (3) Parkinson's syndrome (4) Subclinical aspiration (5) Ataxia (6) Restricted eye movements	• Muscle-strengthening exercises for oral function • Swallowing exercises • Relaxation • Compensatory • swallowing exercises • Huffing
Sphincter palsy	(1) Swallowing reflexes do not occur (2) Swallowing reflex pattern is disturbed (3) Tongue paralysis (4) Failure of the cricopharyngeal muscle to open (5) Laryngeal paralysis (6) Soft palate hemiplegia	• Cold pressure stimulation of the larynx • Cold water drinking training • Surgical therapy or Botox • Intermittent tube feeding

correlated with functional recovery and 1-year survival in patients with CHF.[10] Cachexia may be a factor involved in the development of dysphagia, the clinical manifestation of which is systemic inflammation and associated weight loss.

Systemic inflammation is a major factor in disease-induced anorexia, decreased food intake, and muscle catabolism.[3,4] In addition, skeletal muscle wasting often precedes the onset of cachexia. It is easy to speculate that muscle wasting can lead to impaired swallowing function, and dysphagia induced by hyponutrition, sarcopenia, and cachexia may affect clinical outcomes. However, at this time, there is no evidence that dysphagia is a factor involved in the progression of cachexia. Dysphagia not only develops due to aging, comorbidities, and the major causative diseases of stroke and head and neck disease but it can also occur in the presence of cachexia.

Age-related changes in the swallowing function are referred to as senile dysphagia and are accompanied by a decline in the functional reserve capacity.[36,37] Since age-related sarcopenia has also been found to affect the skeletal muscles involved in swallowing, it decreases the tongue pressure and chewing strength, leads to inadequate food mass formation, and increases the risk of aspiration and choking. Studies in healthy older adults aged 80 years or over have shown that aging delays the swallowing reflex and increases the presence of oropharyngeal residues.[38] Unlike age-related changes, when the disease develops, the ability to compensate for swallowing is impaired, leading to significant dysphagia.[39]

Cancer

Cancer cachexia is heavily modulated by factors such as lipid mobilizing factor and proteolysis-inducing factor released from tumors as well as inflammatory cytokines.[40] Cancer patients commonly develop anorexia. Lymphocytes, mononuclear cells, and macrophages release large amounts of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α.[41] Inflammatory cytokines also have an effect on leptin receptors in the hypothalamus, decreasing appetite and showing leptin-like effects. There are multiple causes of anorexia in patients with cachexia. Inflammatory cytokines and tumor-producing factors contribute to anorexia, increased catabolism, and decreased fat and muscle mass. Cachexia mainly decreases weight and muscle mass, but in rare cases, it may also be caused by dysphagia or gastrointestinal transit problems.[42] When patients with cancer suffer from cachexia, they are less responsive to radiation, chemotherapy, and anticancer therapy and more prone to postoperative complications.[5] Advanced cancer, anticancer therapy, and comorbidities may interfere with anorexia, food intake, and digestive and absorptive capacity.[43] These can exacerbate anorexia because they interfere with both appetite and food intake.

Due to metabolic abnormalities and reduced food intake, cancer cachexia causes weight loss. In patients with cancer cachexia, the eating status is influenced by the type of tumor and various treatment-induced symptoms such as anorexia, pain, and fatigue, so-called nutritional impact symptoms (NIS). NIS associated with weight loss in patients with cancer includes stomatitis, dysphagia (difficulty swallowing), nausea, vomiting, constipation, and taste disturbances.[44] The 2009 ESPEN guidelines indicate that about 50% of patients who lose weight are hypometabolic.[45] With metabolic changes, fatigue, nausea, and anorexia may occur, and weight loss may worsen. Twenty-five to 57% of patients treated for head and neck cancer have a poor nutritional status.[46] Patients with head and neck cancer also lose weight because of inadequate food intake linked with dysphagia.[47] Many patients with cancer experience weight loss and eating disorders during the course of the disease and

Table 3
Characteristics of dysphagia in Parkinson's disease patients and possibilities for intervention.

	Characteristics	Possible interventions
Parkinson's disease	(1) Preceding period • Depressive symptoms • Eating disorders • Tremor and stiffness of the upper limbs (2) Preparatory and oral phase • Tongue movement and mastication disorders • Drooling • Dry mouth (3) Pharyngeal period • Delayed swallowing reflex • Aspiration • Food residue (4) Esophageal phase • Weakening of impulse peristalsis • Gastro-esophageal reflux	• Medication reconciliation • Rehabilitation tube feeding • Food morphology adjustment • Postural adjustment • Exhalation muscle training • Surgical therapy

treatment. In particular, malnutrition in patients with head and neck cancer occurs at approximately 35–60%, with weight loss of 10% or more.[48] In addition, these patients with cancer present with gastrointestinal disturbances, sarcopenia, and anorexia throughout the treatment period.[49]

Dysphagia in patients with cancer is an acute and chronic complication that is associated with clinical outcomes. Most studies of dysphagia have not only focused on neck and head cancers but dysphagia is also seen in patients with other types of cancer. Patients with cancer and with dysphagia frequently have malignancies of the neck and head region. There are three causes of dysphagia in patients with head and neck cancer: damage caused by the tumor itself, damage caused by chemoradiotherapy, and damage caused by surgery. Dysphagia due to cancer includes the obstruction of food passage routes by the tumor and neuropathy due to tumor wetting. Dysphagia due to chemoradiotherapy and surgery is handled differently depending on the treatment. Tumors affect swallowing movements, and their localization and stage determine the severity and frequency of dysphagia.[50–52] Several studies revealed a higher incidence of pre-treatment dysphagia in patients with cervical and head cancers. The prevalence of dysphagia was reported as 28.2%, 50.9%, and 28.9% for oral cavity, pharyngeal, and laryngeal cancer at stage II or higher, respectively.[50] In another retrospective study, the prevalence of oral cavity cancer, pharyngeal cancer, laryngeal cancer, and hypopharyngeal cancer was 5%, 33%, 29%, and 52%, respectively, at all stages.[52] In addition, Stenson et al[51] demonstrated that the dysphagia severity in stage III and above was 28% mild, 34% moderate-to-severe, and 4% severe. Furthermore, in addition to tumor-induced dysphagia, increasing age may be associated with increased dysphagia at the time of evaluation.[53] Dysphagia was also reported in 50.6% of patients with neck and head cancer who underwent surgery and radiation therapy or chemoradiation.[54] Surgical interventions result in anatomical and neurological deficits. Dysphagia and acute toxicity may be accelerated by concomitant chemotherapy, but this has not been adequately reported. A normal swallowing function can be interfered with complications from chemotherapy and cancer.

Lees et al[11] reported that in a regional cancer center, 57% of patients with neck and head cancer at the start of radiotherapy showed weight loss. In addition, the incidence of dysphagia, a causative factor in the development of cancer cachexia, was assessed by a questionnaire and more than 1/3 of all patients had dysphagia. NIS in a patient with mixed cancer population were assessed using a checklist, and it was demonstrated that dysphagia was present in 11.5%.[44] Until now, studies examining dysphagia in patients with cancer have been limited to questionnaires or checklists to assess dysphagia, and no studies have conducted detailed surveys or analyses. Video endoscopic examination of swallowing (VE) and video fluoroscopic examination of swallowing (VF) are gold standards in swallowing assessment.[45–48] VE can diagnose functional abnormalities in the pharyngeal stage and assess organic abnormalities, but it cannot assess swallowing in the oral stage, so VE alone is limited in its assessment of swallowing. In contrast, VF provides an accurate morphologic and functional assessment of the aspiration risk and the presence and severity of dysphagia.

Questionnaires used for the subjective assessment of dysphagia in patients with cancer are personal scales evaluated by patients and clinicians and are inaccurate in assessing dysphagia. There is a marked error in the reporting of subjective and objective assessments of dysphagia; Pauloski et al[49] reported a strong correlation between dysphagia and the VF-assessed swallowing function of patients. On the other hand, Jensen et al[55] reported only a weak correlation between the complaints of dysphagia as assessed by questionnaires and objective ratings. Objective ratings may underestimate the severity of patient-reported dysphagia. The site of impairment is limited to the site of tumor presence and localized area of treatment. There is no evaluation of dysphagia specialized for head and neck cancer, and multiple screening tests are still used. However, it is necessary to consider and evaluate the characteristics of each primary site and the impact of treatment. We believe that it may be useful to use multiple clinical and objective methods to clarify the swallowing function and diagnose dysphagia. At this time, there is insufficient evidence to suggest the possibility of dysphagia due to cachexia in patients with cancer. Dysphagia may not be commonly evaluated in the diagnosis of cachexia. However, patients with cancer may exhibit cachexia-induced dysphagia, and dysphagia is considered to be severe based on muscle atrophy, anorexia, and cachexia. Recognizing that chemotherapy and cancer side effects can impair swallowing function and lead to the further development of cachexia, the assessment and management of dysphagia should be incorporated into the diagnosis and treatment plan for cachexia.

COPD

The World Health Organization (WHO) predicted that COPD, a chronic inflammatory disease of the lungs and whole body, mainly caused by smoking, would become the third leading cause of death worldwide by 2020.[56] Patients with COPD have elevated levels of pro-inflammatory cytokines (C-reactive protein, IL-6, and TNF-α), which are associated with decreased exercise tolerance and the lean body mass.[57] Expression of the pro-inflammatory transcription factor nuclear factor-kappaB is enhanced in skeletal muscle of patients with low-weight COPD.[58] It has been suggested that systemic inflammation is more marked in patients with cachexia, which also leads to anorexia. In addition, the secretion of leptin, an appetite suppressant, is increased in patients with COPD. The clinical consequences of cachexia are related to both systemic inflammation and weight loss.[59] It is also logical to consider that muscle atrophy leads to dysphagia. In COPD, there is airflow obstruction and pulmonary hyperinflation, which is not completely reversible and can contribute to COPD exacerbation, leading to potentially fatal complications and comorbidities.[60] In COPD, repeated exacerbations aggravate the primary disease and increase the frequency of cachexia.[6] Wagner et al[61] reported that about 25% of patients with COPD develop cachexia, and the complication of cachexia in patients with COPD increases the risk of death.

Patients with COPD are often complicated by dysphagia. Cough and dysphagia are the main symptoms leading to a suspicion of dysphagia. In patients with COPD, 65% were reported to have subjective dysphagia.[62] Mokhlesi et al[63] reported that patients with COPD frequently used spontaneous protective swallowing maneuvers, such as a longer duration of airway closure and earlier laryngeal closure relative to the cricopharyngeal opening. Furthermore, in patients with respiratory disease, ingestion, and swallowing may exacerbate the shortness of breath and
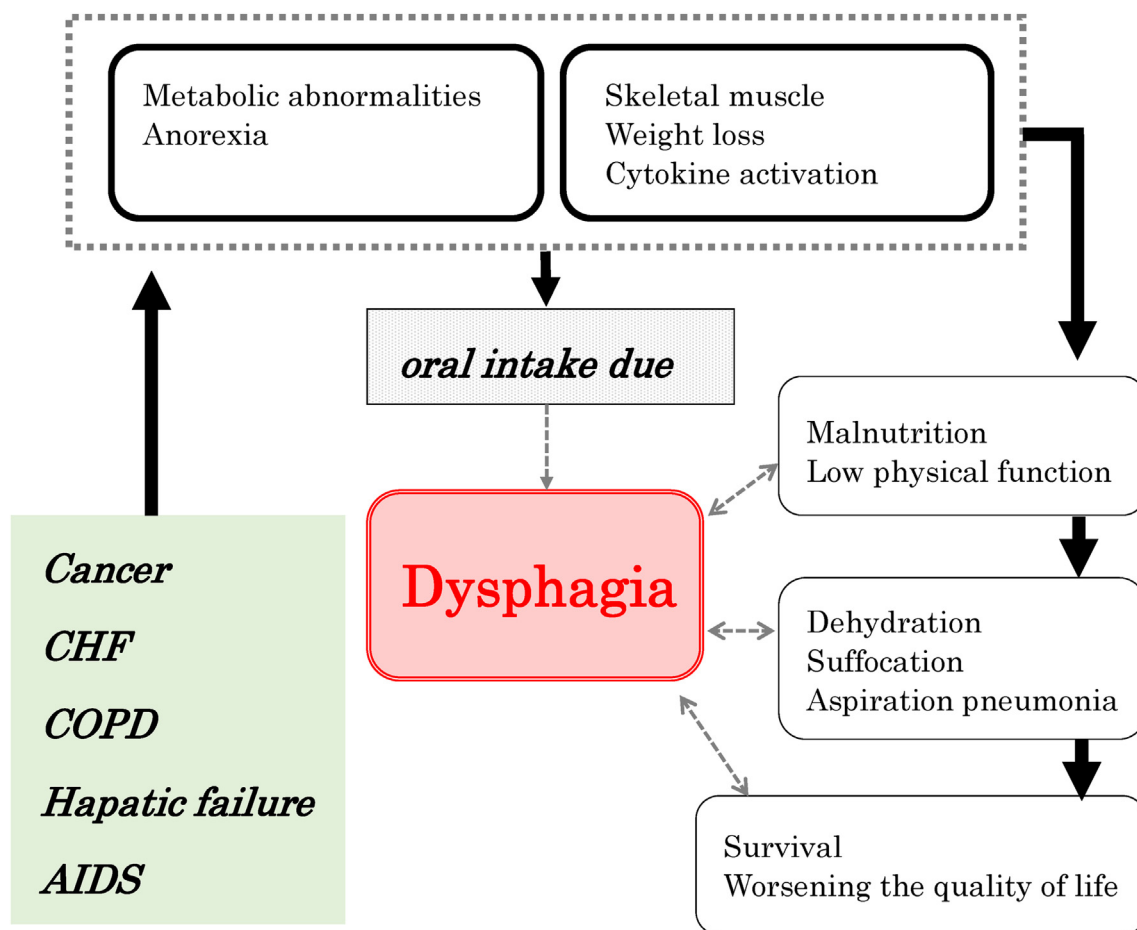
Fig. 2. Possible association between the signature chronic disease factors and dysphagia. Cachexia occurs with chronic wasting disease. Metabolic abnormalities, anorexia, weight loss, and skeletal muscle loss are associated with malnutrition. These symptoms may result in decreased oral intake and have a major effect on dysphagia. Dysphagia is likely to be associated with dehydration, asphyxia, aspiration pneumonia, life-threatening illness, and a poor quality of life.

other symptoms, which are considered to result in a poor nutritional status. Dysphagia has a significant impact on the nutritional status; Karand et al[64] reported that all low-weight patients with COPD had dysphagia. In general, patients with COPD do not have specific neurological or structural etiologies that contribute to dysphagia; COPD is modulated with undernutrition and impaired exercise tolerance to a lesser extent.[65] Dysphagia has been implicated in increased risks of nutritional problems and aspiration and may affect swallowing-related muscle groups. The incidence of aspiration, laryngeal penetration, and dysphagia in patients with COPD was 42%, 28%, and 85%, respectively.[44] It has been suggested that the presence of dysphagia is one factor causing COPD,[66] and a recent systematic review noted the importance of the swallowing process in patients with COPD in six of seven studies.[67] COPD exacerbations may be predicted by unstable swallowing dynamics with aspiration. Complications such as aspiration pneumonia, airflow obstruction, and dehydration due to dysphagia may contribute to COPD exacerbation.[68] Recent studies focused on the correlation between dysphagia and COPD and the association between swallowing and breathing coordination and exacerbation.[66,69] Multiple case–control studies reported that patients with COPD have a high prevalence of dysphagia, with 84% of patients with moderate-to-severe COPD and 20% with dysphagia.[70,71] Terada et al[72] also reported that dysphagia significantly induces exacerbations. Furthermore, evaluation with VF suggested that patients with COPD had a longer duration of pharyngeal stage damage during swallowing compared with healthy subjects.[73] Using VF, Cvejic et al[74] showed that patients with stable and moderate COPD aspirate large amounts of fluid during swallowing, and the contents are more likely to enter the larynx. Although VF and VE are reliable methods

for detecting dysphagia, from a practical standpoint, they cannot be performed for all patients, and there are currently no validated swallowing tests for patients with COPD. Depending on which assessment method is used in a study, an underestimation of dysphagia may occur. However, the number of studies showing an association between COPD and dysphagia is small, and there have been no randomized controlled trials. Considering the differences in definitions, assessment methods, and selection criteria, more research is still needed to clarify whether there is a direct association between cachexia and dysphagia in COPD.

CHF

Heart failure is a syndrome of repeated progression and exacerbation. Heart failure is considered a major socioeconomic health problem, present in up to 2% of the population in developing countries.[7] The prevalence of congestive heart failure ranges from 5% to 15%.[75] The development of heart failure is associated with a high 5-year mortality rate of more than 50%.[7] Cachexia linked with heart failure is defined as cardiac cachexia and it leads to involuntary and progressive weight loss.[7] Muscle mass loss due to cachexia has been shown to occur in cardiac muscle as well as skeletal muscle.[76] Hyponutrition and cachexia are present in many patients with heart failure and are associated with an increased quality of life and mortality. Heart failure is one of the most common reasons for hospitalization,[77] and cachexia is associated with higher readmission rates.[78] Overall, 8%–42% of heart failure patients are considered to have cardiac cachexia.[75] Sundaram et al[79] showed that 1-year mortality was 20%–30% higher in patients with cachectic heart failure. Levine et al[80] showed that blood levels of TNF-α are increased in patients with heart failure. In patients with heart failure, receptors for

IL-6 and TNF-α are increased.[81] TNF-α and IL-1 are considered to act directly on the brain to decrease appetite.[82] The pathogenesis of heart failure is mainly influenced by inflammatory cytokines.

The presence of cardiac cachexia may worsen the nutritional status. Several clinical studies have reported the prevalence of hyponutrition in patients with CHF to be 54%–69%.[83,84] Our group[85] reported that malnutrition in heart failure patients undergoing cardiac rehabilitation was approximately 56%. Resting energy expenditure may increase in the presence of cardiac cachexia,[86] and 10%–20% of patients with heart failure exhibit anorexia.[87] Without adequate energy intake, the nutritional status is likely to deteriorate. Anorexia occurs in patients with heart failure for several reasons. Heart failure symptoms, such as respiratory distress and fatigue, lead to decreases in activity and ADL, and skeletal muscle loss. As a result, food intake may decrease and the nutritional status may deteriorate. Hyponutrition is common in all situations in which these occur. Hypotrophy is characterized by decreased skeletal muscle strength with functional impairment.[88] Pineda-Juares et al[89] found that the combination of resistance exercise and branched-chain amino acids could appropriately manage cachexia and sarcopenia in heart failure patients. They showed that resistance exercise alone can produce clinical and physical improvements even in the absence of supplementation with branched-chain amino acids. Sarcopenia is widely considered to necessitate appropriate nutritional management and physical therapy in addition to the treatment of the primary disease.[90] Several review articles described the usefulness of combined exercise and nutritional intervention for elderly patients with sarcopenia.[91]

However, there has been almost no research on the association between cardiovascular disease (CHF) and dysphagia. Ferraris et al[92] reported that patients with preoperative heart failure are in the stage of OD. Furthermore, dysphagia associated with congestive heart failure has been suggested to prolong the hospital stay of CHF patients by 1.8 times.[77] Furthermore, patients with heart failure develop dysphagia during hospitalization.[10] Dysphagia is frequently observed in elderly patients with heart failure and has a significant impact on clinical outcomes in patients with heart failure and is closely associated with stroke and neck and head disease. It is necessary to investigate dysphagia concurrently with the evaluation of heart failure and cardiac cachexia. This is because a decreased swallowing function can be caused by aging, intestinal malabsorption, and decreased energy and protein intake, which can lead to the development or worsening of dysphagia.[77,93] More detailed studies are needed to determine whether dysphagia causes worsening cachexia and a poorer nutritional status in patients with heart failure.

Fig. 2 presents a possible association between the signature chronic disease factors and dysphagia.

Pharmacotherapy

Cachexia

Currently, there is no standard pharmacotherapy with proven efficacy for cachexia.[94] There are also few high-quality clinical studies examining the efficacy of nutritional and exercise therapies for cancer cachexia, and no standard interventions have been established.[95–97] Progesterone preparations to increase appetite and corticosteroid have been tried to improve the nutritional status of patients with cachexia, with weight gain but no improvement in muscle mass.[98] Non-steroidal anti-inflammatory drugs and eicosapentaenoic acid, which have anti-inflammatory effects, are not effective alone.[99,100] Cachexia is a complex metabolic disorder and differs from a single disease, requiring a learned approach.

Ghrelin receptor agonist (anamorelin hydrochloride) has been studied in two large randomized phases III trials in Europe and the USA (HT-ANAM-301, HT-ANAM-302) and several trials in Japan. The results showed that anamorelin effectively increases body weight and appetite in non-small cell lung, gastric, pancreatic, and colorectal cancers with

Table 4
Drugs and main side effects affecting each phase of feeding and swallowing.

Feeding and swallowing	Drug	Side effects
Advance Period	Anticonvulsants Antipsychotics Anti-anxiety drugs	• Impairment of cognitive abilities
Preparatory phase Oral phase	Anticholinergics Anticholinergic agonists	• Xerostomia • Decreased saliva production
Pharyngeal phase	Benzodiazepines	• Inability to coordinate the pharyngeal region • Aspiration
Esophageal phase	Drugs affecting smooth muscle and neurotransmitters	• Esophageal injury • Esophagitis • Gastro-esophageal reflux

cancer cachexia.[101] Anamorelin hydrochloride is approved only in Japan and is used exclusively for cancer cachexia in non-small cell lung, gastric, pancreatic, and colorectal cancer. On the other hand, clinical trials of anamorelin hydrochloride have shown no improvement in physical function in patients, despite an increase in lean body mass. The contribution of the drug to patients' overall quality of life and survival has not been adequately assessed. It is essential to recognize that an increase in skeletal muscle mass with drug treatment does not necessarily improve physical function or quality of life.[102]

Dysphagia

Drug side effects can affect feeding and swallowing. For example, sedatives and psychotropic drugs reduce the swallowing reflex and cause subclinical aspiration. Drugs that act on the central nervous system, such as antipsychotics, anxiolytics, and antidepressants, directly inhibit the nervous system responsible for swallowing, causing motor and functional impairment and sensory disturbances in the oral cavity and pharynx, thus affecting all phases of feeding and swallowing. Drugs that affect all phases of feeding and swallowing and their main side effects affecting each phase of feeding and swallowing are listed in Table 4. Drugs with anticholinergic properties have been reported to cause xerostomia by decreasing the level of consciousness and saliva production.[103] Drugs that improve dysphagia include amantadine hydrochloride, angiotensin-converting enzyme inhibitors, and cilostazol. Amantadine hydrochloride has been reported to promote dopamine release from dopamine nerve endings in the basal ganglia and reduce the incidence of pneumonia.[104] Angiotensin-converting enzyme inhibitors improve the swallowing and coughing reflexes by inhibiting substance P degradation. They have been shown to reduce pneumonia morbidity in patients with stroke.[105] Cilostazol has been shown to reduce pneumonia after stroke.[106] Increasing dopamine and substance P levels in the brain with drugs have been reported to trigger the swallowing reflex and prevent dysphagia.[107] Drugs causing dysphagia should be reviewed for discontinuation or dose reduction as appropriate.

Table 5
Comparison of clinical advantages of VF, VE, and checklist.

APPLY	VF	VE	Checklist
Initial evaluation	○		○
Oral function	○		○
Pharyngeal and laryngeal functions	○	○	○
Esophageal function	○		○
Dynamic evaluation	○	○	
Secretion evaluation		○	
Anatomic deviations		○	
Biofeedback		○	
Simplicity		○	○
Exposure		○	
Time constraint		○	○

Comparison of clinical advantages of VF and VE

VF aims to determine the diagnosis of the condition and factors contributing to the disorder and determine treatment strategies to control the disease. VF can also be used to evaluate all processes from the oral cavity to the esophagus,[108] but the issue of radiation exposure need to be considered as it involves radiation. VF is considered suitable for diagnosing aspiration, but it is unclear whether aspiration can be accurately diagnosed in the examination setting. VE should be used to observe the pharynx and larynx at rest and during swallowing to examine swallowing dynamics.[109] On the other hand, VE cannot be used to observe movements in the oral cavity, esophagus, and pharyngeal phase due to whiteout. However, compared with VF, there is no radiation exposure, no prolonged examination time, and no restriction on the examination location. VE is the most informative of the adjunctive diagnostic procedures for dysphagia. Both VF and VE have advantages, and the purpose of the examination should be clearly defined and implemented, leading to appropriate training and guidance. Table 5 summarizes and compares the clinical advantages of the swallowing evaluation methods.

Conclusions

At present, it has not been verified whether dysphagia is directly caused by cachexia. Reduced oral intake due to weight loss and poor appetite in cachexia may affect dysphagia. The assessment of clinical swallowing needs to be performed routinely; few studies have descriptively reported on dysphagia in patients with CHF and COPD. Methods for assessing dysphagia vary markedly from study to study, which may lead to an underestimation of dysphagia. Because dysphagia is a significant problem associated with the clinical outcome, its accurate assessment and careful management should be incorporated into the diagnosis and treatment plan for cachexia.

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Declaration of competing interest

None Declared.

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