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Review

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Stroke-Related Sarcopenia: Pathophysiology and Diagnostic Tools

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HIGHLIGHTS

- Stroke and sarcopenia are associated, hindering functional recovery.
- The conventional sarcopenia consensus has limitations in diagnosing stroke-related sarcopenia.
- Diagnostic criteria tailored to stroke patients' physical traits are needed.

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ABSTRACT

Sarcopenia is characterized by the progressive loss of muscle mass and strength and can be categorized as either primary or secondary. Patients who have experienced a stroke may develop sarcopenia, which can adversely impact their functional recovery. The pathophysiology of sarcopenia related to stroke involves nutritional deficiency, disuse atrophy, denervation, and metabolic disturbance. Various evaluation tools are available to diagnose this condition, assessing skeletal muscle mass, muscle strength, and physical function. However, due to the limitations of traditional sarcopenia diagnostic criteria in the context of stroke, there is pressing need to establish diagnostic standards that accurately reflect the disabilities experienced by patients with stroke.

Keywords: Stroke; Sarcopenia; Pathophysiology; Diagnosis

INTRODUCTION

Sarcopenia is a condition characterized by the gradual loss of muscle mass and strength, as defined by the International Working Group on Sarcopenia [1]. It is categorized into primary and secondary sarcopenia. Primary sarcopenia refers to muscle function loss that occur acutely, often during or following a period of acute illness or immobility, and it may also develop gradually with aging. Secondary sarcopenia, on the other hand, can be caused by any disease or disability that limits physical activity. Disease-related sarcopenia accelerates muscle atrophy and becomes integrated into the disease process, seen in cerebrovascular events. Following a stroke, patients may develop sarcopenia due to alterations in muscle tissue and structure [2-5]. The pathophysiology of post-stroke sarcopenia includes factors such as inflammation, physical inactivity, and nutritional deficiencies [6]. Sarcopenia significantly affects an individual's mobility and overall quality of life [7,8]. The condition increases the risk of falls, disability, and hospitalization due to diminished muscle strength and function, which can impair balance and coordination [9]. Studies have shown that stroke survivors are at a high risk of developing sarcopenia, which can further complicate their recovery and rehabilitation [10]. For these reasons, there has been growing attention in recent years to the changes in muscle tissue characteristics following a stroke.

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Author Contributions

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Traditionally, stroke-related disability has been primarily attributed to brain injury, with less emphasis placed on the structure, metabolism, and function of muscle tissue. It has been observed that the number of motor units decreases following a cerebral infarction, likely due to issue in transmission from spinal α-motor neurons, which in turn leads to adaptive changes in muscle tissue [11]. Stroke patients exhibit significantly lower muscle mass in both limbs than healthy adults [12]. The impairment in the central cortex alone cannot fully account for the bilateral reduction in limb strength [11]. With advancements in high-resolution imaging, there is stronger evidence supporting muscle atrophy as a primary mechanism contributing to hemiplegia and weakness [13]. Sarcopenia can adversely impact the functional recovery of stroke patients. The muscle weakness and diminished physical function associated with sarcopenia can hinder the ability to regain motor functions and independence after a stroke. Rehabilitation efforts may be less effective in the presence of sarcopenia [14]. This paper reviews the latest insights into the pathogenesis and evaluation tools of stroke-related sarcopenia.

EPIDEMIOLOGY

Stroke is a leading cause of morbidity and mortality worldwide. According to the World Health Organization, approximately 13.7 million people experience a stroke each year globally [15]. Sarcopenia is commonly observed in stroke patients, with a recent systematic review and meta-analysis reporting a 42% pooled prevalence of stroke-related sarcopenia [16]. The risk of developing sarcopenia in stroke patients is influenced by several factors, including the severity of the stroke, oral intake, comorbidities, and walking ability [17-20]. For example, a higher National Institute of Health Stroke score, a longer intensive care unit stay, and the presence of dysphagia or malnutrition, all increase the risk of stroke-related sarcopenia. In contrast, spasticity appears to protect against muscle loss, thereby reducing the risk of sarcopenia [21]. However, the role of age as a risk factors remains a subject of debate [18,21,22].

PATHOPHYSIOLOGY

Disuse atrophy is a significant contributor to muscular weakness following a stroke. It is characterized by rapid reduction in muscle mass, alterations in muscle tissue (including a shift towards fibers more susceptible to fatigue), neurogenic changes that affect muscles on both sides of the body, and a catabolic imbalance [22]. The pathological mechanisms underlying sarcopenia in stroke patients are complex, involving multiple interrelated factors. Sarcopenia, defined by the progressive loss of muscle mass, strength, and function, can be significantly worsened by a stroke through various pathways.

Nutritional deficiency

Nutritional deficiency is a major problem in stroke patients. Post-stroke dysphagia, which affects 24.3%–52.6% of stroke survivors, exacerbates this problem and can adversely impact recovery, rehabilitation, and overall outcomes [23]. In addition to oral dysphagia, other factors contributing to nutritional deficits in these patients include reduced appetite, immobility, cognitive impairments, and inadequate dietary intake [24]. These issues can detrimentally influence muscle mass, strength, body composition, and the functional status of the patients. It is crucial to recognize that nutritional status often declines in stroke patients due to persistent undernutrition and feeding difficulties during hospitalization.

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Consequently, tissue consumption is accelerated in these patients due to inadequate nutrient supply and anabolic disorders.

Disuse atrophy

Disuse atrophy, particularly following a stroke, involves the loss of muscle mass and strength due to reduced physical activity or immobility. Patients who have suffered a stroke are particularly susceptible to disuse atrophy due to a significant reduction in movement and physical function post-stroke [25]. When muscles are subjected to prolonged periods of disuse, they enter catabolic pathways, leading to an increase in proteolysis that surpasses protein synthesis, ultimately resulting in muscle atrophy. Additionally, stroke-induced immobility can alter muscle fiber composition [26]. Typically, there is shift from type I (slow-twitch) fibers, which are more resistant to fatigue, to type II (fast-twitch) fibers, which fatigue more quickly. This transformation exacerbates weakness and diminishes endurance [27]. Muscle atrophy can also lead to joint contractures, pressure ulcers, and an increased risk of falls. Weakened muscles are less able to support the body and maintain balance [28].

Denervation

Stroke-related disability is caused by brain injury and disruption of the upper motor neuron pathways, leading to hemiparesis [29]. In age-related sarcopenia, the loss of motoneurons has been proposed as a potential cause of muscle wasting. The neurological deficits and limited mobility lead to structural changes in skeletal muscles, initiating disuse atrophy. As early as four hours after a stroke, the number of motor units in the affected limb begins to decrease, and this reduction persists into the chronic phase [30]. In patients with stroke, significant alterations are observed in the nonparetic limb, including reductions in muscle mass, declines in muscle strength, increases in adipose tissue deposition, and impaired glucose tolerance, despite the absence of direct paralysis. These changes occur within a similar temporal framework as those observed in the paretic limb [31]. Typically, muscle loss on the nonparalytic side can be reversible; rehabilitation may help recover muscle function and address metabolic changes [32].

Metabolic disturbances

Skeletal muscle plays a critical role in maintaining glucose homeostasis, primarily through insulin-mediated signaling pathways that facilitate glucose uptake. A decrease in muscle mass, reduces insulin responsiveness, leading to insulin resistance and disrupted glucose regulation [33]. Additionally, increased sympathetic tension is associated with the activation and secretion of proinflammatory cytokines. These cytokines can inhibit the synthesis of myofilament and alter the composition of striated muscle cells. Furthermore, they enhance catabolic signaling and suppress anabolic activity following a stroke, contributing to muscle degradation and atrophy [27,34].

EVALUATION TOOLS

In 2010, the European Working Group on Sarcopenia in Older People (EWGSOP) established three key diagnostic criteria for sarcopenia, focusing on muscle mass, muscle strength, and physical performance [35]. Low muscle mass (LMM) is defined as a skeletal muscle mass index below 8.90 kg/m^2. Low muscle strength (LMS) is indicated by a hand-grip strength of less than 30 kg for men and 20 kg for women. Low physical performance (LPP) is characterized by a gait speed slower than 0.8 m/s. A diagnosis of sarcopenia

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is confirmed when a patient exhibits LMM in conjunction with either LMS or LPP. The EWGSOP categorized sarcopenia into three stages: Pre-sarcopenia, which involves the presence of LMM alone; Sarcopenia, which combines LMM with either LMS or LPP; and Severe sarcopenia, which includes all three criteria. In 2018, the EWGSOP revised these guidelines, placing greater emphasis in muscle strength as the primary diagnostic parameter for sarcopenia [36]. The updated guidelines recognize muscle strength as a more reliable indicator of muscle function and a better predictor of adverse health outcomes compared to muscle mass alone. Sarcopenia is considered probable when LMS is present and is confirmed by evidence of low muscle quantity or quality.

The Asian Working Group for Sarcopenia (AWGS) has focused on creating consensus guidelines tailored to the Asian population, drawing on regional studies. In 2014, the AWGS introduced an algorithm for diagnosing sarcopenia in Asians, which was influenced by the EWGSOP but featured specific cutoff values. The suggested cutoff values for diagnosing sarcopenia are as follows [2]:

- Muscle mass: 7.0 kg/m^2 for men and 5.4 kg/m^2 for women using dual-energy X-ray absorptiometry (DEXA), and 7.0 kg/m^2 for men and 5.7 kg/m^2 for women using bioelectrical impedance analysis (BIA).
- Handgrip strength: < 26 kg for men and < 18 kg for women.
- Usual gait speed: < 0.8 m/s.

In May 2019, the AWGS revised its diagnostic algorithm, keeping the previous sarcopenia definition but updating several criteria [12]:

- Handgrip strength: < 28.0 kg for men and < 18.0 kg for women.
- Physical performance tests: the 6-m walk test (cutoff speed ≤ 1.0 m/s), Short Physical Performance Battery (SPPB, cutoff score ≤ 9), and 5-time chair stand test (cutoff time ≥ 12 seconds).

The AWGS 2019 also introduced new tools for identifying sarcopenia cases:

- Calf circumference: < 34 cm for men and < 33 cm for women.
- SARC-F questionnaire: a tool assessing five components (Strength, Assistance in walking, Rising from a chair, Climbing stairs, and Falls), with a score of ≥ 4 indicating sarcopenia.
- SARC-CalF: combines SARC-F and calf circumference, where a score of ≥ 11 suggests sarcopenia.

The AWGS 2019 guidelines introduced the term “possible sarcopenia” for patients showing LMS with or without reduced physical performance, while reserving the term “sarcopenia” for cases where low appendicular skeletal muscle mass (ASM) is present alongside LMS or LPP. If all three (low ASM, LMS, and LPP) are present, the diagnosis is severe sarcopenia. The diagnostic consensus for sarcopenia is presented in detail in **Fig. 1**.

These criteria are difficult to apply to stroke patients. The following methods can be used for diagnosing sarcopenia in stroke patients.

Skeletal muscle mass

DEXA is the standard method for assessing for the skeletal muscle mass, and it is the most frequently used modality for measuring body composition in patients with stroke [37]. Magnetic resonance imaging and computed tomography (CT) scans provide a more precise

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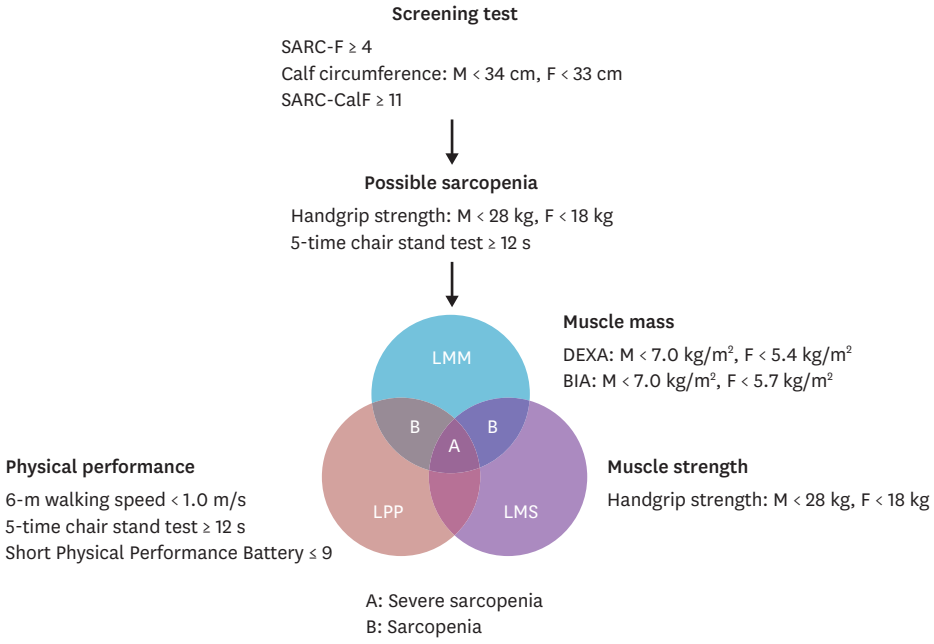

Fig. 1. Algorithm for sarcopenia evaluation based on the Asian Working Group for Sarcopenia 2019 guidelines. SARC-F, sarcopenia screening questionnaire; M, male; F, female; SARC-CalF, sarcopenia screening questionnaire adding calf circumference; LMM, low muscle mass; LMS, low muscle strength; LPP, low physical performance; DEXA, dual-energy X-ray absorptiometry; BIA, bioimpedance analysis.

differentiation between muscle tissue and intramuscular fat by evaluating the cross-sectional area of the extremities, unlike DEXA scans. In a study of 30 stroke patients, muscle mass in the lower limbs was assessed using both DEXA and CT scans six months post-stroke. The results from DEXA showed a 3%–4% reduction in lean tissue mass in the affected limbs and thighs, whereas CT scans indicated a 20% reduction in the muscle area of the mid-thigh of the affected limb compared to the unaffected limb. The study also indicated that hemiplegic muscle atrophy and increased intramuscular fat contribute to dysfunction in chronic hemiplegic stroke patients [38]. Currently, BIA is widely used to estimate body composition and measure muscle mass. BIA assesses the body's electrical impedance, which is the resistance to an alternating electrical current passed through the body [39]. This method helps determine the amounts of lean mass, fat mass, and body water content, providing valuable information for clinical assessments and monitoring.

Strength of skeletal muscle

The commonly used methods for assessing muscle strength include grip strength measurement, the knee flexion and extension test, and peak expiratory flow measurement. Among these, grip strength is considered a reliable an straightforward indicator for evaluating upper limb muscle strength [40]. However, in patients with hemiplegia resulting from a stroke, measuring muscle strength on the affected side may be impractical, and the results might not provide meaningful data for diagnosing sarcopenia. Some studies have investigated the extent of tissue injury and skeletal muscle metabolic damage in patients with acute ischemic stroke by measuring maximum grip strength in both the contralateral and hemiplegic hands [41]. Nevertheless, grip strength alone may not suffice as a comprehensive assessment of overall body and lower limb function. To ensure the reliability and accuracy of physical fitness evaluations, it is crucial to guide patients to maintain a standardized posture during measurements [42].

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Physical function

Gait speed is a simple and established criterion for diagnosing sarcopenia. However, due to hemiparesis or asymmetric weight-bearing, 52%–85% of stroke patients experience difficulties with gait, rendering gait speed measurements of limited diagnostic value in this group [43]. Assessments such as the 4-m usual walking speed test (with a cutoff speed of ≤ 0.8 m/s), the SPPB (with a cutoff score of ≤ 8 points), the timed up and go test (with a cutoff time of ≤ 20 seconds), and the 400-m walk test are effective for evaluating walking ability in patients with sarcopenia. Nevertheless, these tests are challenging to administer to stroke patients [35,44]. Several tests are available to assess function and independence in daily activities or stroke patients. These include the Modified Barthel Index, Modified Rankin Scale, Motoricity Index, Rivermead Motor Assessment Gross Functional Scale, Trunk Control Test, and Fugl-Meyer Assessment, which are useful in evaluating the physical abilities of these patients. However, there is scant research exploring the correlation between these tests and sarcopenia. Future studies that demonstrate the relevance of these test results in assessing the severity of sarcopenia could help establish diagnostic criteria for stroke-related sarcopenia.

CONCLUSION

Understanding the pathophysiological characteristics of sarcopenia and stroke reveals a significant correlation between the two conditions, which may exacerbate the disabilities associated with these diseases. The traditional diagnostic criteria for sarcopenia are inadequate for diagnosing stroke-related sarcopenia, highlighting the need to establish diagnostic standards that accurately reflect the disabilities experienced by stroke patients.

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