

Sarcopenia in stroke—facts and numbers on muscle loss accounting for disability after stroke

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Abstract Stroke is the third leading cause of death and the leading cause of disability in Western countries. More than 60% of patients remain disabled, 50% of patients suffer from some hemiparesis and 30% remain unable to walk without assistance. The skeletal muscle is the main effector organ accountable for disability in stroke. This disability is, however, traditionally attributed to the brain injury itself and less attention is paid to structural, metabolic and functional aspects of muscle tissue. Hemiparetic stroke leads to various muscle abnormalities. A combination of denervation, disuse, inflammation, remodelling and spasticity account for a complex pattern of muscle tissue phenotype change and atrophy. While the molecular mechanisms of muscle degradation after stroke are only incompletely understood, a stroke-related sarcopenia may be concluded. Reinnervation, fiber-type shift, disuse atrophy and local inflammatory activation are only some of the key features to be addressed. Despite the importance for optimum post stroke recovery, stroke-related sarcopenia is not recognised in current guidelines for stroke therapy and rehabilitation. A total of not more than 500 patients forms the basis for all available evidence on clinical muscle changes after stroke. A lack of robust evidence on muscle pathology after stroke and on treatment strategies becomes apparent that needs to be addressed in an interdisciplinary integrated approach.

Keywords Sarcopenia · Stroke · Muscle · Recovery · Myopenia

1 Introduction

Sarcopenia is primarily a disease of the elderly. In view of the constantly older growing population of our modern society, it is therefore a very timely approach to address those muscle-related problems in a newly designed and specific journal [1]. Accumulation of data on structural, metabolic and functional characteristics of skeletal muscle will provide a solid platform to cross-fertilize between clinical and basic science specialties. Thus, the impact of skeletal muscle on disease progression or recovery processes may become apparent. Until now, this often goes unrecognised or underestimated as minor side effect of the primary disease.

Stroke may serve as a prime example how skeletal muscle may be of utmost importance for the outcome of patients and yet limited attention is focussed on metabolic and functional alterations in skeletal muscle after stroke. An interdisciplinary approach on the peripheral metabolic implications of stroke is warranted to complement brain- and neuro-specific perspectives to achieve an integrated perspective on patients with stroke.

2 Stroke—a growing problem

Stroke is one of the leading causes of death in industrialised countries ranging just behind cardiac- and cancer-related causes. Stroke incidence varies across Europe between 100 and 700 events per 100,000 inhabitants being highest in Eastern European countries (Lithuania and Poland) and lowest in south Europe (Italy and Spain) [2]. Stroke

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incidence in the US has been estimated with 795,000 events per year of which approximately one quarter are recurrent strokes [3]. In 2008, a stroke prevalence of 7,000,000 patients has been estimated for the US with an average of one patient dying from stroke every 4 min [4]. Stroke is also the single greatest cause of disability in the adult population in modern society [5]. Even with optimal acute therapy, about two thirds of patients remain in a state of incomplete recovery after stroke [6], 15–30% are permanently disabled and 20% require institutional care at 3 months after onset [3]. Rehabilitation efforts are pivotal to optimize functional recovery after stroke and the benefit of rehabilitation is beyond doubt. Yet, assignment of patient to rehabilitation is largely dependent of the structured health care system and may vary between countries. A US national survey in 2005 observed that only 31% of stroke survivors received outpatient rehabilitation [3]. This number was considerably lower than expected if clinical practice guideline recommendations for all stroke patients had been followed.

3 Stroke and skeletal muscle changes

Long-term disability is the most frequent complication after stroke with 50% of patients suffering from some hemiparesis and 30% being unable to walk without assistance [7]. Hemiparetic stroke leads to muscle abnormalities with a combination of denervation, disuse, remodelling and spasticity that may account for a complex pattern of phenotype shift and atrophy. Structural adaptive changes in muscle tissue were observed to start as early as 4 h after cerebral infarction. They may be related to disrupted synaptic transmission of the muscle innervating motor neurons and lead to the reduction of motor unit numbers [8]. Interestingly, muscle weakness develops as well in the unaffected limb within 1 week after paretic stroke [9].

3.1 Stroke and fiber-type shift

Human skeletal muscle fibres have great adaptive potential; yet, molecular mechanisms of the atrophy and phenotype shift after stroke are not known in great detail. In normal ageing, muscle tissue changes are characterised by a shift in fiber-type distribution with decrease in fast-twitch muscle (MHC type IIa and IIb) fibers and increase in mitochondria-rich slow-twitch (MHC type I) muscle fibers that results also in reduction of muscle strength. Thus, between 30 and 60 years of age, muscle strength decreased by 18% and between the seventh and ninth decade another 20% were lost [10]. This fiber-type shift results from motor unit denervation and subsequent reinnervation from adjacent intact muscle fibres. In contrast to the age-dependent shift from fast-twitch to slow-twitch fibres, an inverse shift

towards increased fast-twitch MHC type II isoforms with more reliance on anaerobic metabolism has been observed in stroke [11]. This fiber-type shift was a strong predictor of impaired functional capacity such as gait deficit severity after stroke. To what degree this stroke-induced denervation and reinnervation contributes to stroke specific phenotype shift of skeletal muscle tissue needs further evaluation.

3.2 Stroke and disuse atrophy

Inactivity and immobilisation after stroke are also important factors as muscle unloading produces a multitude of (mal-) adaptive responses of muscle tissue. Hence, it has been reported that patients with acute stroke were physically active for less than 40 min a day during hospitalisation [12]. Inactivity results, among others, in insulin resistance, which not only affects glucose-dependent energy metabolism but also leads to decreased anabolic stimulation from insulin. Only 10 days of bed rest in healthy older adults has been shown to induce a 30% decrease in muscle protein synthesis and a 6% reduced leg lean mass that results in 16% reduced muscle strength [13]. Notably, nutritional status is often reduced already at stroke occurrence [14], undernutrition continues while hospitalised [15] and feeding difficulties often persist thereafter. Hence, in stroke patients, an even accelerated tissue wasting due to combined insufficient nutritional supply and anabolic failure may be more realistic.

The long-term muscle changes such as loss in muscle mass, reduction of cross-sectional area and increased intramuscular fat deposition occur between 3 weeks and 6 months in both paretic and non-paretic limbs [16, 17]. One would expect that the loss of muscle mass after stroke is accompanied by weight reduction although replacement of lean tissue by increased fat mass has been observed [18]. In fact, according to a recent population-based study from the Lund stroke registry with a cohort of 305 patients, weight loss of over 3 kg within a short-term (4 months) and a medium-term (1 year) period after stroke was found in about one quarter of patients [19]. However, a recent systematic review reported about the presence of malnutrition ranging from 8 to 49% among stroke patients [20] that would contribute to weight loss as well. It may need further pathophysiologic studies to decide if these processes qualify as development of cachexia according to the current definition [21] or if these processes represent sarcopenia [22].

3.3 Stroke-related sarcopenia

While sarcopenia may occur in the course of normal ageing, specific disease-related sarcopenia (or myopenia) should be considered in conditions where accelerated muscle wasting

occurs as part of a disease process. Recently, some papers described sarcopenia in sepsis and cancer [23, 24]. It needs to be determined whether disease-specific mechanisms are responsible for distinct types of muscle tissue degradation or whether a common pathophysiologic pathway accounts for a more or less uniform muscle catabolic process in those diseases [25]. Given the stroke-induced alterations in muscle tissue characteristics, a specific stroke-related sarcopenia might be concluded that resembles age-dependent sarcopenia in some characteristics but contrasting it in others.

Interestingly, although the skeletal muscle is the main effector organ accountable for disability in stroke, this disability is traditionally attributed to the brain injury itself. Considerable less attention is paid to the secondary abnormalities of muscle atrophy, metabolic and contractile capacity and local inflammatory milieu. A recent systematic review was undertaken to accumulate all clinical study data on changes in skeletal muscle mass, volume or cross-sectional area in stroke patients [26]. Out of 17,042 related publication hits from the initial database search, mere 14 studies were identified with a total of 490 patient participants that were studied either cross-sectionally or in longitudinal studies. Emerging data suggest that skeletal muscle (mal-) adaptive processes importantly contribute to disability after stroke and that exercise interventions may clearly be useful strategies to prevent muscle wasting and restore physical capacity and mobility after stroke. More work is warranted to define the importance of this peripheral catabolic aspect of stroke physiology.

4 Muscle wasting in stroke—not appreciated in the guidelines

To date, the issue of stroke-related sarcopenia is not recognized with all its clinical implications in relevant European or North American stroke guidelines [27, 28]. Despite clinical studies observed muscle loss after stroke contributing to disability and adverse outcome after stroke, the guideline recommendations do not consider prevention of muscle wasting after stroke as relevant target. Also rehabilitation-orientated guidelines do not consider prevention of muscle wasting or restored anabolic capacity as relevant interventional targets [29, 30]. This currently under-represented aspect will need to be appreciated more thoroughly within an interdisciplinary concept of stroke rehabilitation. Certainly, physical activity in the form of exercise rehabilitation belongs to the standard therapy after stroke [31], prevention or restoring of muscle metabolic abnormalities will substantially contribute to this. Thus, a clinical study in older acute stroke patients revealed that nutritional supplementation within the first week in hospital has a beneficial effect for maintaining an adequate

body mass and body composition [32]. While the former study used global high caloric and protein supplementation, selective supplementations such as of essential amino acids may have advantages in preserving muscle metabolic integrity and function [33]. We are only at the beginning to define optimum nutritional strategies in this context with regard to amount, timing, content, etc. Muscle metabolic abnormalities and sarcopenia are challenging areas for future work towards an integrated and interdisciplinary approach on stroke patients.

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Conflicts of interest The authors declare that they have no conflict of interest.

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