

Determinants of muscle preservation in individuals with cerebral palsy across the lifespan: a narrative review of the literature

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Abstract

In individuals with cerebral palsy (CP), smaller muscle and atrophy are present at young age. Many people with CP also experience a decline in gross motor function as they age, which might be explained by the loss of muscle mass. The clinical observation of muscle wasting has prompted a comparison with sarcopenia in older adults, and the term accelerated musculoskeletal ageing is often used to describe the hallmark phenotype of CP through the lifespan. However, there has been very little research emphasis on the natural history of ageing with CP and even less with respect to the determinants or prevention of muscle loss with CP.

Considering the burgeoning interest in the science of muscle preservation, this paper aims to (i) describe the characteristics of accelerated musculoskeletal ageing in people with CP, (ii) describe the pathophysiology of sarcopenia and parallels with CP, and (iii) discuss possible therapeutic approaches, based on established approaches for sarcopenia.

Keywords Cerebral palsy; Sarcopenia; Muscle; Exercise

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Introduction

Cerebral palsy (CP) is the most common paediatric-onset physical disability, with a prevalence of 1.7–3.1 per 1000 livebirths in high-income countries and higher prevalence in low-income countries.^{1,2} Cerebral palsy is caused by an insult to or malformation of the developing brain that affects motor control centres and leads to alterations in growth and development. Although the brain lesion that causes CP is non-progressive, it affects overall health and especially mobility throughout the lifespan.^{3,4} Following the central nervous system lesion, the damage to the descending pathways causes paresis—a reduction or failure of voluntary activation and muscle over activity that can be described as spasticity, spastic dystonia, and spastic co-contraction. Although the

primary brain lesion is static, these neural changes result in a cascade of secondary musculoskeletal complications that are progressive, including soft tissue contracture and bone deformity.^{5,6} Research pertaining to the structure and physiology of skeletal muscle of children and young adults with CP has highlighted several abnormalities. *In vivo* studies of muscle in ambulant individuals with CP report structural differences between CP and typically developed (TD) muscle including reduced muscle size^{7–10} and abnormal proportions of contractile and non-contractile tissue.^{11–13} While loss of muscle mass and function is apparent at higher ages in the general population, smaller muscle and early atrophy are already present at young age in individuals with CP.^{14,15} Individual differences determine the extent to which this impacts physical performance, mobility, and functional ability.

In fact, approximately 75% of the individuals with CP who were once mobile eventually stop ambulating.¹⁶ It is also well documented that even high-functioning children with CP are at increased risk to lose ambulatory skills or turn to assistive devices in adulthood,¹⁷ which leads to substantial declines in functional skills, activities of daily living and/or mobility, and independence.^{18–21} These clinical observations have prompted a comparison with older adults without CP, and the term ‘accelerated musculoskeletal ageing’ has been proposed to describe the hallmark phenotype of CP through lifespan.²² However, there has been very little research emphasis on the natural history of ageing with CP and even less with respect to the determinants or prevention of muscle loss in CP.

In an attempt to stimulate research pertaining to clinically observed, age-related muscle atrophy and weakness, the term ‘sarcopenia’ was first introduced in 1989.²³ Despite the exponential growth in this area of research over the past 30 years,²⁴ there have been substantial obstacles with adopting a consensus definition for the diagnosis of sarcopenia in clinical settings. Although the initial definition of sarcopenia was limited to describing age-related muscle atrophy, muscle loss can also occur with disuse, chronic inflammation, and inadequate macronutrient and micronutrient intake or is associated with acute and chronic disease, all of which are not necessarily age related.^{25,26} Therefore, the term (primary) sarcopenia indicates muscle wasting related to ageing, while ‘secondary sarcopenia’ refers to muscle loss related to disuse, inflammation, or malnutrition.²⁵ In the elderly, however, the aetiology of sarcopenia can be multifactorial so the distinction between ‘primary and secondary sarcopenia’ can be difficult to make.²⁵

Considering the burgeoning interest in the science of muscle preservation in individuals with CP, it is time to consider the knowledge and evidence related to sarcopenia in the general population as it pertains to people with CP. This paper aims to (i) describe the characteristics of accelerated musculoskeletal ageing in people with CP, (ii) describe the pathophysiology of sarcopenia and parallels with CP, and (iii) discuss possible therapeutic approaches—what can we learn from approaches in sarcopenia prevention/treatment?

Characteristics of muscle and muscle growth in people with cerebral palsy: is cerebral palsy characterized by accelerated musculoskeletal ageing?

In 2010, the European sarcopenia consensus definition was published,²⁵ which (re)defined sarcopenia as a condition in which at least two of these three criteria apply: (i) low muscle mass, (ii) low muscle strength, and/or (iii) low physical

performance. In this paragraph, we discuss characteristics of muscle and muscle growth in people with CP and examine whether the criteria of sarcopenia can also be applied to individuals with CP.

Muscle size and composition

Muscle size (e.g. cross-sectional area or volume) are important morphological properties and indicators of muscle force-producing capacity,²⁷ as well as insight into the amount of metabolically active lean tissue available for glucose storage and metabolism.²⁸ In individuals with CP, the muscles in the impaired limb are smaller than the muscles in the unimpaired limb, and both are smaller compared with a muscle of a TD child.⁷ Cross-sectional studies investigating muscle volume in individuals with CP and TD peers report differences in muscle size that are evident early in development, with as much as 22% smaller calf muscle size in children with CP present by preschool age.²⁹ The differences in muscle volume of ambulant individuals with CP compared with TD peers increase with age to over 45% smaller calf muscle size in young adults with CP.²² In individuals with unilateral CP, the often considered ‘unaffected limb’ has muscle that is more similar to the impaired limb with smaller volume and altered muscle quality compared with TD peers.³⁰ Muscle size differences between individuals with CP and TD peers have also been reported for the volume of nine large lower-limb muscles in adolescents and cross-sectional area of the psoas muscle in adults.^{8,31} Among adults, a previous study using computed tomography demonstrated that the psoas muscle in CP is significantly smaller and less dense, indicating greater muscle fat infiltration and lower muscle quality.³²

Muscle is composed of contractile and non-contractile tissues. The contractile tissue is the force-generating tissue that causes movement. It is composed of sarcomeres, the building blocks that form muscle fibres, and bundles of muscle fibres that form fascicles. The contractile tissue is highly metabolic. The non-contractile tissue comprises predominantly connective tissue in series (i.e. tendons) and parallel (aponeuroses and muscle cell framework), as well as intermuscular and intramuscular fat. Muscles of the lower limb of individuals with CP have greater connective tissue fraction¹² and more intermuscular and intramuscular fat on magnetic resonance imaging and computed tomography and have altered echo intensity parameters, indicative of increased non-contractile tissue, on B-mode ultrasound compared with TD peers.^{11,13,30,33} Therefore, the proportion of muscle volume that includes the contractile tissue may be less. *Ex vivo* studies of muscle from ambulant and non-ambulant children with CP compared with TD children further report reduced myofibre cross-sectional area,³⁴ altered fibre type distribution,³⁵ shorter and stiffer muscle cells,³⁶ and longer and fewer sarcomere in series.³⁷

Reduced muscle volume with greater connective tissue and fatty infiltration in individuals with CP greatly reduces the force generation capacity of muscle³¹ and also reduces the pool of metabolic lean tissue compared with TD individuals. Moreover, altered muscle fibre and sarcomere structure further reduces the force and movement generating capabilities. To date, no studies have quantified muscle structure and composition of the upper limb in individuals with CP or investigated the muscle changes throughout adulthood with CP.

Muscle growth

There is limited published information describing muscle growth in individuals with CP. To date, there has been only one longitudinal study describing the growth of lower-limb muscle in children with CP.¹⁵ It was shown that in pre-school-aged children with CP, growth of the calf muscle was significant at 12 months follow-up, even after lower-limb botulinum toxin treatment (an established treatment to reduce muscular hyperactivity due to spasticity in children and adults with CP). However, the overall muscle growth of the spastic muscle in children with CP over 12 months was 60% lower than in TD peers. Recent cross-sectional studies report calf muscle volume increases linearly with age in CP; however, the muscle volume increased to a lesser extent than in TD children.^{10,14} In a combined group of children with unilateral and bilateral CP, muscle growth, as indicated by the slope of the age–volume relationship, was almost half that of TD children.¹⁴ Moreover, the muscles of children with unilateral CP developed at a slower rate than the muscles of children with bilateral CP, with muscle growth at 23% and 65% of the TD muscle growth rate, respectively.¹⁰ The lower muscle growth rate results in a greater disparity of calf muscle volumes between the CP groups as children progress into adolescence and adulthood.

The limited research investigating muscle growth in individuals with CP has focused on the early childhood years. This period often includes standard care treatments that aim to reduce spasticity and slow contracture development and maintain walking ability in these children.³⁸ Treatments including serial casting and intramuscular botulinum toxin injections may also compromise muscle growth.^{39–41} However, current studies have not differentiated between the effects of treatments and the underlying mechanisms that lead to reduced growth in CP in general, as compared with TD children. Surgical interventions for lower-limb soft tissue contracture reduce muscle growth, but muscle volume was found to recover 1 year after surgery.⁴²

The natural history of muscle growth and decline with age in individuals with CP remains unknown. Moreover, the specific reasons for reduced longitudinal muscle growth, development of contractures, and peripheral factors

responsible for muscular weakness also remain poorly understood. It is plausible that this may stem from the brain lesion causing CP, with the impact of reducing total muscle fibre number in an impaired muscle.⁴³ Furthermore, genetic alterations have been identified in spastic CP muscle, which give rise to competing pathways for muscle hypertrophy and decrease in anabolic growth factors. The efficiency of protein uptake and synthesis (among other building processes) remains unknown in CP.

Strength and function

Structural abnormalities in the muscle among individuals with CP, including reduced muscle size and abnormal composition, combined with altered neural control (e.g. increased co-contraction and selective activation^{44,45}), contribute to reduced muscle strength and power compared with TD individuals.^{31,46–48} Muscle strength varies widely not only among individuals but also among disability severity, as classified by the Gross Motor Function Classification System (GMFCS; function deteriorates from levels I to V).⁴⁹ The muscle strength of children classified as GMFCS levels I and II ranges between 50% and 100% of predicted normal for all muscle groups of the lower extremity except ankle dorsiflexors (which is lower). For children classified as GMFCS level III, muscle strength is less than 50% of predicted normal for all muscle groups of the lower extremity except knee extensors (which is higher).⁵⁰

While loss of muscle mass and function is expected in the general ageing population, gradual loss of physical performance and functional ability is present even at young ages in individuals with CP. Hanna *et al.*⁵¹ showed that stability of the gross motor function trajectories varies over time when children and adolescents with CP transition into young adulthood. In children classified as GMFCS levels III–V, the average gross motor function score peaks before it declines when children become adolescents and young adults. These findings indicate that adolescents classified as GMFCS levels III–V are at risk of losing motor function and physical performance. Throughout adulthood, a gradual decline in functional ability is reported across all GMFCS levels.⁵² Approximately 75% of individuals with CP included in the study by Murphy *et al.*¹⁶ who were once mobile eventually stopped ambulating. Adolescents with CP enter adult life with reduced strength and functional reserve, with one-third of adults with CP experiencing a decline in walking ability before the age of 35 years.¹⁸ It is also well documented that even high-functioning children with CP are at increased risk to lose ambulatory skills or turn to assistive devices in adulthood,¹⁷ which leads to substantial declines in functional skills, activities of daily living and/or mobility,¹⁹ and ultimately a loss of independence.^{18–21}

In children and young adults with CP, lower-limb muscle strength is closely related to independent mobility with muscle adaptations resulting in reduced walking speed and distance, as well as more frequent tripping and falling.^{4,16} The reduced trajectory of muscle strength through development may be the critical factor that determines functional capacity and mobility in CP.²²

The pathophysiology of sarcopenia: a multifactorial concept caused by a combination of interrelated factors

Several factors underlie the loss of muscle mass and function with advanced age in TD individuals, such as anabolic resistance, impaired muscle quality, and nutritional factors. This section describes these factors in sarcopenia and analogues what is known in people with CP.

Anabolic resistance and contributing factors like inactivity, inflammation, and oxidative stress

Muscle mass is the result of a balance between continuous synthesis and degradation of skeletal muscle proteins. Net protein balance is defined as the difference between skeletal muscle protein synthesis (MPS) and breakdown (MPB). A positive net protein balance (i.e. when MPS exceeds MPB) can result in the accretion of skeletal muscle proteins (anabolism). Conversely, a negative net protein balance (i.e. MPB exceeds MPS) will result in a loss of skeletal muscle protein (catabolism). During the ageing process, protein turnover declines,⁵³ and a blunted response of MPS to anabolic stimuli in a meal has been reported.⁵⁴ This so-called anabolic resistance is suggested as the major contributor to loss of muscle mass in TD adults and elderly.⁵⁵ Several factors can contribute to anabolic resistance, such as inactivity, chronic inflammation (inflammaging), and oxidative stress.^{56,57}

Indeed, a more sedentary lifestyle plays an important role in the development of sarcopenia.⁵⁸ However, ageing is also characterized by an increased incidence of enforced bed-rest periods, secondary to injury or disease. These periods of total inactivity contribute directly to the sarcopenia process as it has been shown that the rate of muscle mass loss is accelerated in older persons undergoing a period of bed rest.⁵⁹ Disuse atrophy is characterized by a reduction in muscle fibre cross-sectional area. The consequences of inactivity-induced muscle wasting include reduced strength and muscle quality, with deleterious effects on quality of life and independence in daily activities. Furthermore, this reduction in metabolically active lean tissue results in decreased capacities of whole-body glucose storage and metabolism,^{28,60} which contributes to insulin resistance, and a lower whole-body

metabolic rate.⁶¹ Muscle disuse has been studied after a variety of interventions including bed rest, casting, limb suspension, and spaceflight. Whenever human MPS has been measured after inactivity, a marked decline has been observed in 24 h MPS, because of lowered fasted MPS and a reduced postprandial MPS response to an anabolic stimulus. The reduced MPS occurs relatively early in immobilization (within 10 days of bed rest) and does not decline further.⁵⁹ Thus, anabolic resistance is not always age related. It can also be a direct consequence of disuse and deconditioning. In young adults who have been typically developing, a reduction in physical activity through cast-induced immobilization of the legs blunts basal and amino-acid stimulated rates of MPS.^{62–64} Thus, it is apparent that disuse induces anabolic resistance in skeletal muscle regardless of age. Recent work also indicates that even short-term abrupt sedentary behaviour, leading to a reduced relative loading of skeletal muscles, resulted in loss of muscle mass in the legs.⁶⁵

In addition, oxidative stress and chronic inflammation play important roles in muscle atrophy.⁶⁶ The interaction of these factors affects the balance between MPS and MPB, inducing skeletal muscle cell death (apoptosis), which leads to significant loss of muscle mass. The state of oxidative stress seems to trigger the pathogenesis of muscle wasting in chronic diseases.⁶⁷ The deleterious effect of oxidative stress on the muscle can also be explained through its participation to the low-grade inflammation status by triggering the release of inflammatory cytokines or by participating to the reduced sensitivity of muscle to leucine anabolic action.⁶⁸ Elevated levels of low-grade inflammation induced by oxidative stress are detrimental to skeletal muscle in humans,⁶⁹ as well as in animal models.⁷⁰ Age-related low-grade inflammation has been associated with a decrease in muscle mass and strength⁷¹ and a loss of physical function.⁷²

Analogue cerebral palsy

To the best of our knowledge, there are currently no studies that have examined anabolic resistance in people with CP. However, children with CP have one of the most sedentary lifestyles across paediatric disabilities.⁷³ From 2 to 3 years of age, children with CP show significantly more sedentary behaviour than TD children and, not surprisingly, GMFCS level correlates with sedentary behaviour, with more sedentary behaviour occurring in those with levels IV and V.⁷⁴ Decreased activity levels not only lead to muscle weakness, disuse muscle atrophy, and muscle shortening but also lead to further activity limitations, which prompt a vicious circle of inactivity and disuse.⁷⁵ Despite the lack of studies to directly measure anabolic response in children with CP, the low physical activity levels and related disuse make it plausible that children with CP have decreased anabolic responses to dietary amino acids and protein, to a similar extent seen in the elderly with sarcopenia.

In children with CP, oxidative stress may be caused by a deficiency in vitamin and food intake, environmental factors (i.e. passive smoking and fruit juice intake), and epileptic seizures.⁷⁶ However, the few studies that have examined oxidative stress markers in children with CP have yielded inconclusive findings. Aycicek and Iscan⁷⁶ showed that children with CP have increased lipid hydroperoxide levels (a marker for oxidative stress) and decreased antioxidant levels when compared with TD children. The authors concluded that children with CP have an impaired oxidative/antioxidative balance when compared with TD children. In contrast, Kulak *et al.*⁷⁷ showed that children with CP have similar lipid hydroperoxide levels as TD children. At the same time, some antioxidant enzyme levels were found to be lower in children with CP, whereas other antioxidant enzyme levels were higher, which led the authors to conclude that children with CP do not show elevated levels of oxidative stress compared with their TD peers.

Impaired muscle quality, that is, muscle strength per mass unit, and muscle function with underlying factors like intramuscular fat, impaired mitochondrial function, muscle fibre type changes, and neuromuscular innervation

Apart from the decrease in muscle mass, which is reflected by a decrease of up to 50% in the size and number of muscle fibres from 20 to 90 years of age,⁷⁸ there are also composition changes in the muscle that occur with age. Specifically, there is a selective age-related atrophy of type 2 fibres (glycolytic fibres, predominant in fast-twitch muscles).⁷⁹ Moreover, there is an age-dependent increase in muscle fat content, which is known to be positively correlated with whole-body fat.⁸⁰ Age-related muscle fat infiltration can be part of the sarcopenia process, as it is associated with lower muscle strength⁸¹ and an increased risk of developing mobility limitations.⁸² Moreover, specific loss of α -motor neurons⁸³ leads to multiple processes of denervation–reinnervation of muscle fibres and consequently to the decline in coordinated muscle action and reduction in muscle strength. Another factor in the pathogenesis of sarcopenia is the age-related decrease in mitochondria number and function. This is the consequence of an alteration in the expression of genes encoding mitochondria protein,⁸⁴ a decrease in mitochondria protein synthesis,⁸⁵ a decrease in mitochondria oxidative capacity, and ATP production rates.⁸⁴ This can have a major impact on endurance capacity and muscle fatigue, which in turn can contribute to the decreased physical function observed in elderly. A new study suggests that mitochondrial dysfunction, reduced insulin sensitivity, and reduced physical endurance are related, at least in part, to physical inactivity and to increases in adiposity rather than to ageing alone.⁸⁶

Analogue cerebral palsy

Muscles of the lower limb of ambulant individuals with CP have greater connective tissue fraction¹² and more intermuscular and intramuscular fat^{11,13,33,87} compared with TD peers. Furthermore, Johnson *et al.*¹³ showed that children with quadriplegic CP (GMFCS III–V) had 2.3-fold higher intermuscular adipose tissue in the mid-thigh muscles than control subjects, and this was related to their low levels of physical activity. At a muscle fibre level, Ito *et al.*⁸⁸ showed a type 1 fibre predominance in spastic muscles of individuals with CP and a type 2b fibre deficiency with significant variation in fibre size. It is also reported that spastic muscle in CP show myofibrillar disorganization in poorly defined areas (moth-eaten fibres), fibres with rounded contours in cross section (vs. normal polygonal contours), and in some cases, an increased extracellular matrix and fibrotic increase in passive stiffness.⁴³ Taken together, these studies show that children with CP have lower muscle quality than TD children, which might contribute to impaired muscle function in this particular patient group.

Nutritional factors: deficiencies of protein and vitamin D

Although older adults may decrease their overall energy intake, the actual need for certain macronutrients and micronutrients may increase with age. Inadequate nutrition or malabsorption and/or maldigestion are suggested as one of the underlying mechanisms involved in the onset or progression of sarcopenia.²⁵ Certain nutrients are referred to as musculoskeletal nutrients, that is, protein, calcium, vitamin D, magnesium, and phosphorus.⁸⁹ The relation between nutrients and muscle parameters has been extensively reviewed by Mithal *et al.*⁹⁰ for protein, vitamin D, and the B vitamins and by Robinson *et al.*⁹¹ for antioxidants and long-chain polyunsaturated fatty acids. However, nutritional recommendations for sarcopenia mainly apply to consideration of adequate protein intake and adequate vitamin D status,⁹² as the evidence for these nutrients is most evident. Considering the role of malnutrition in the pathophysiology of sarcopenia,²⁵ adequate energy intake is important to prevent muscle loss.

Adequate protein intake is especially relevant for stimulation of MPS in conditions of anabolic resistance. This is intuitive, as muscle is the largest protein reservoir in the body, with muscle proteins being replaced at a rate of 1–2% per day. A dietary intake study in a large cohort showed that protein intake decreases with age.⁹³ High daily protein intake in healthy older adults is associated with a reduced loss of muscle mass, as shown in several cohort studies in older people.⁹⁴ Indeed, individuals with sarcopenia showed a lower intake of dietary protein compared with non-sarcopenic individuals.^{95,96} Among 55- to 77-year-old

ambulatory men and women, 14 days of controlled dietary protein intake at the recommended level (recommended dietary allowance: 0.8 g protein/kg body weight (bw)/day) resulted in a significant decrease of the mid-thigh muscle area and a decrease in urinary nitrogen excretion.⁹⁷ This also implies that a protein intake greater than the recommended dietary allowance in elderly is required to maintain nitrogen balance, fat-free mass, and muscle mass.⁹⁷ Explorative studies suggest that healthy older people may require a minimum protein intake of 1.0 to 1.5 g/kg bw/day to achieve a null nitrogen balance and to preserve muscle mass, strength, and function.⁹⁸ A recent consensus paper by the dietary protein needs with ageing group advised that older adults should consume 1.0–1.2 g protein/kg bw/day, and even higher amounts are recommended for older adults who are malnourished.⁹⁹

Moreover, protein intake varies throughout the day. This is important as it is hypothesized that 25–30 g high-quality protein per meal is needed for adequate stimulation of MPS to counteract anabolic resistance with ageing.¹⁰⁰ Habitual protein intake is highest at lunch or evening meals but is especially low at breakfast.^{101–104} The habitual low-protein intake at breakfast may therefore prevent maximal MPS. One recent publication indicated that the distribution of protein intake over the day differs between frail and non-frail community-dwelling seniors, with the lowest intake at breakfast in the frail.¹⁰⁵

The lack of specific (anabolic) nutrients is responsible for the loss of muscle mass; however, an adequate caloric intake is also needed to facilitate metabolic processes. If nutrients intake is insufficient to meet the needs, resulting in malnutrition, body fat and muscle will be catabolized to provide energy.¹⁰⁶ Therefore, meeting the daily energy recommendation is important for the maintenance of muscle mass and physical performance.

Age-related declines in vitamin D receptor can also contribute to the loss of muscle strength.¹⁰⁷ The importance of adequate vitamin D status is recognized, but low serum vitamin D levels are also commonly reported. Houston *et al.*⁹⁴ reported inadequate levels (<50 nmol/L 25(OH)D) in 75% of older women and 50% of older men (InCHIANTI cohort). The vitamin D intake through nutrition was found to be low in elderly in Europe,¹⁰⁸ and inadequate vitamin D intake is indeed a health concern. Also, the reduced time spent outdoors and the skin's decreased ability to make vitamin D contribute to low vitamin D status with ageing. Several observational studies found an association between vitamin D status and muscle strength, physical performance (e.g. balance and chair stand), physical activity, fall occurrence, and activities of daily living.^{109,110} Describing the exact working mechanism of vitamin D and its receptor in muscle is outside the scope of this review (for a review on this topic, see Hamilton, 2009¹¹¹). In short, vitamin D is involved in the transcription of a range of proteins, including those involved in

calcium metabolism, which is critical for skeletal muscle function. It is also widely believed that vitamin D has a rapid effect on membrane calcium channels thereby being a critical modulator of muscle function.¹¹¹ Another mechanism by which vitamin D acts on muscle is through increasing the sensitivity of MPS to an anabolic stimulus, as shown for leucine in muscle cells under vitamin D-deficient and vitamin D-supplemented conditions.¹¹² Vitamin D thus seems essential for muscle function.

Analogue cerebral palsy

Some of the nutritional factors that contribute to the development of sarcopenia might also play a role in the muscle function of people with CP. The prevalence of malnutrition, which may result in an inadequate protein intake, is also elevated in the CP population.¹¹³ Adequate dietary protein intake may therefore be a critical key factor for maintaining skeletal muscle mass in people with CP. This is supported by the findings of Arrowsmith *et al.*¹¹⁴ who found low total body protein levels (as measured by neutron activation analysis) in children with spastic quadriplegic CP. This could be the result of reduced muscle mass due to inactivity, or, malnutrition coupled with the inactivity and consequently decrement in muscle volume. There are many possible reasons people with CP fail to consume enough protein to meet their needs. Medical conditions (food processing and swallowing problems), physical and mental disabilities that limit shopping and food preparation, and food insecurity due to financial and social limitations are commonly reported reasons.¹¹³

Despite the feeding and swallowing difficulties in a great proportion of the children with CP, different studies showed no differences in protein intake between children with CP and their TD peers.^{115–118} However, to date, it remains unclear whether children with CP have similar protein requirements as TD children. Many people with CP participate in intensive (strengthening) exercise programmes, and because exercise causes muscle micro-damage, it is important to replace and rebuild this tissue to allow for hypertrophy and strength increases.¹¹⁹ Therefore, it may be argued that for children with CP, it is crucial that a regular dietary intake of high-quality proteins is necessary and that there is even a higher need for these proteins than for children without CP.

Adequate vitamin D intake is essential for preservation of muscle strength and function. Individuals with CP may be at heightened risk for hypovitaminosis D-induced osteopenia and impaired bone mass accrual. The risk of secondary health complications associated with or exaggerated by the combination of insufficient vitamin D, chronic sedentary behaviour, and obesity may also be higher. Indeed, about 30% of the children with CP have insufficient vitamin D status^{120,121}, however, a major difficulty in comparing literature on this topic is the use of different cut-off points for vitamin D

deficiency. Therefore, it is difficult to say whether the percentages in CP are high or similar compared with the general population in which a deficiency prevalence of 2–60% is reported.^{122,123} Although present across all GMFCS levels, vitamin D deficiency is more prominent in children classified at GMFCS levels IV and V, who might have reduced outdoor activity. One of the factors that could contribute to vitamin D deficiency is the use of anticonvulsants.¹²⁴ About 41% of children with CP have epilepsy, and anticonvulsant use is common. It can therefore be assumed that vitamin D deficiency is common in this population. Moreover, in a recent study with CP adults, more than 50% were either vitamin D insufficient or deficient, and abdominal adiposity was a strong independent predictor for low vitamin D levels.¹²⁵

Therapeutic approaches in sarcopenia with focus on (i) protein (quantity per day and at each meal; protein quality), (ii) vitamin D, and (iii) combination with exercise

Recommending dietary modifications, nutritional supplements, and exercise therapy separately or in combination can be appropriate steps to stimulate muscle growth and combat muscle deterioration in people with CP. Maximizing muscle mass can improve functionality, strength, endurance, and general metabolic health. Based on the pathophysiology of sarcopenia and prevalent nutritional deficiencies, therapeutic approaches with protein, vitamin D, and/or exercise have been applied. This section discusses what we can learn from these approaches for possible future interventions in individuals with CP.

Protein interventions

It is well established that dietary protein ingestion stimulates skeletal MPS and inhibits protein breakdown, resulting in a positive protein balance and net muscle mass gain.^{126,127} Net protein balance is maintained by ingestion of protein-containing meals, which results in systemic hyperaminoacidaemia that is stimulatory for the synthesis of new proteins.^{128–130} The ingested protein dose and source dictates the amplitude and duration of the rise in essential amino acids in the blood, which, in turn, affects the degree of MPS.^{126,131} In addition to increasing the total dose of protein or (essential) amino acids in a meal,¹³² a diminished anabolic responsiveness with ageing can be overcome by increasing the proportion of the amino acid leucine,¹³³ especially at low-protein intake.¹³⁴ Only one study measuring MPS was performed in sarcopenic older adults and demonstrated

an increase of MPS after a leucine-enriched whey protein supplement.¹³⁵

Vitamin D

While the recommendations for older sarcopenic adults are in favour of vitamin D supplementation, randomized controlled trials (RCTs) on muscle strength show non-conclusive results. Both positive effects^{136–138} and absence of effects^{139–141} were observed with vitamin D supplementation. These contradictory results may be attributed to the differences in study design, for instance, baseline vitamin D levels, vitamin D dosing schedule (daily, weekly, or monthly), the dosage of vitamin D supplemented, or the duration of the intervention. Supplementation of at least 800 IU (20 µg) showed, however, an effect on muscle strength.^{136,137} The evidence to support vitamin D supplementation for falls and fracture prevention is more apparent, indicating a beneficial effect of vitamin D supplementation.^{142,143} Based on five RCTs involving 1237 participants, Bischoff-Ferrari *et al.*¹⁰⁹ concluded that vitamin D supplementation appears to reduce the odds of falling by 22% compared with patients receiving calcium supplements or placebo. It has been suggested that this beneficial effect of vitamin D on falling could be explained by 1.25 hydroxyvitamin D binding to a highly specific nuclear receptor in muscle tissue, leading to improved muscle function and thereby reduced risk of falling. In a 2 month intervention of elderly ambulatory women, vitamin D plus calcium supplementation improved body sway by 9% when compared with calcium supplementation alone.¹⁴⁴ Similarly, musculoskeletal function increased by 4–11% in institutionalized elderly women after an intervention with vitamin D and calcium compared with calcium alone. Moreover, the combination of adequate vitamin D and anabolic leucine optimized the MPS response in vitamin D-deficient muscle cells.¹¹² Along the same lines, sufficient baseline 25(OH)D levels and protein intake may be required to increase muscle mass as a result of an intervention with a vitamin D and protein supplement in sarcopenic older adults.⁹⁶

Exercise

The synergistic effect of protein ingestion with exercise potentiates the muscle synthetic response, swinging net balance in favour of muscle protein accretion,¹⁴⁵ thereby permitting muscle hypertrophy when practised frequently over time.¹⁴⁶ Regular exercise may also help normalize some aspects of age-related mitochondrial dysfunction and, in turn, improve muscle function.⁸⁶

Exercise is known to improve muscle strength and function in both the young and the elderly. An updated meta-analysis by Sherrington *et al.*¹⁴⁷ showed that exercise as a single

intervention can prevent falls in community-dwelling older people. In particular, exercise programmes that challenge balance and are of a high intensity have larger effects. It thus seems that exercise alone can already help preventing falls in (healthy) elderly. However, it is also known that protein ingestion after a single bout of resistance-type exercise stimulates muscle protein accretion during post-exercise recovery. Nutrition in combination with exercise is considered optimal for maintaining muscle function.¹⁴⁸ Consequently, it is believed that protein supplementation can augment the effects of resistance-type exercise training. Cermak *et al.*¹⁴⁹ performed a systematic review to define whether this is indeed the case. Based on 22 RCTs that included 680 subjects, they concluded that protein supplementation after prolonged (>6 weeks) resistance-type exercise training has a positive effect on fat-free mass and one repetition maximum leg press strength in younger and older subjects. This suggests that a combination of nutrition with exercise could be optimal for maintaining muscle function.¹⁴⁸

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Although comparable nutritional intervention studies in people with CP are lacking, a recent systematic review has highlighted that there is preliminary evidence that strength training leads to muscle hypertrophy in children and adolescents with CP.⁴⁸ However, nutritional supplementation in

combination with resistance training or a physical activity intervention has not been investigated in people with CP.

Conclusions

In this review, we highlight the evidence for early and accelerated musculoskeletal ageing in CP, which may be comparable with sarcopenia among older adults without CP. Given the fact that nutritional interventions (combined with exercise training) have shown promising effects for mitigating sarcopenia and improving muscle mass and function, future studies should investigate the effect of these interventions as a primary preventive strategy among individuals with CP.

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Conflict of interest

None declared.

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