Handsfield *et al.*
BMC Musculoskeletal Disorders (2022) 23:233
https://doi.org/10.1186/s12891-022-05110-5

BMC Musculoskeletal Disorders

REVIEW

Open Access

Muscle architecture, growth, and biological Remodelling in cerebral palsy: a narrative review

Geoffrey G. Handsfield[1*], Sîan Williams[2,3], Stephanie Khuu[1], Glen Lichtwark[4] and N. Susan Stott[5]

Abstract

Cerebral palsy (CP) is caused by a static lesion to the brain occurring in utero or up to the first 2 years of life; it often manifests as musculoskeletal impairments and movement disorders including spasticity and contractures. Variable manifestation of the pathology across individuals, coupled with differing mechanics and treatments, leads to a heterogeneous collection of clinical phenotypes that affect muscles and individuals differently. Growth of muscles in CP deviates from typical development, evident as early as 15 months of age. Muscles in CP may be reduced in volume by as much as 40%, may be shorter in length, present longer tendons, and may have fewer sarcomeres in series that are overstretched compared to typical. Macroscale and functional deficits are likely mediated by dysfunction at the cellular level, which manifests as impaired growth. Within muscle fibres, satellite cells are decreased by as much as 40–70% and the regenerative capacity of remaining satellite cells appears compromised. Impaired muscle regeneration in CP is coupled with extracellular matrix expansion and increased pro-inflammatory gene expression; resultant muscles are smaller, stiffer, and weaker than typical muscle. These differences may contribute to individuals with CP participating in less physical activity, thus decreasing opportunities for mechanical loading, commencing a vicious cycle of muscle disuse and secondary sarcopenia. This narrative review describes the effects of CP on skeletal muscles encompassing substantive changes from whole muscle function to cell-level effects and the effects of common treatments. We discuss growth and mechanics of skeletal muscles in CP and propose areas where future work is needed to understand these interactions, particularly the link between neural insult and cell-level manifestation of CP.

Background

Cerebral palsy

Cerebral palsy (CP) is one of the most common causes of acquired physical disability in childhood, and the most common cause of physical disability in developed nations [1], with an occurrence of between 1.5 to 4 per 1000 live births [2–5]. Worldwide, there are estimated to be 17 million people living with CP, at least 80% of whom will live into their sixth decade [6]. Cerebral palsy was first identified as a separate disorder in the 1800s, with seminal works by orthopaedic surgeon Dr. William Little describing the secondary musculoskeletal deformities consequent to abnormal events at birth [7, 8]. Early definitions attempted to link cerebral palsy with specific pathologies and etiologies [9]. However, a more encompassing definition came in 1964, when Bax described cerebral palsy as 'a disorder of posture and movement due to a defect or lesion of the immature brain' [10]. Mutch et al. in the 1990s extended this definition of CP to 'an umbrella term, covering a group of non-progressive, but often changing, motor impairment syndromes secondary to lesions or anomalies of the brain arising in the early stages of development' [11]. This definition recognised that CP covers many etiologies and that, while the disorder of posture and movement is permanent and unchanging, the motor impairments are often progressive. In 2007, a group of international collaborators refined this further to recognise other disturbances often seen in CP [12]. Here, CP was defined as "a group

*Correspondence: g.handsfield@auckland.ac.nz
[1] Auckland Bioengineering Institute, University of Auckland, Auckland CBD, Auckland 1010, New Zealand
Full list of author information is available at the end of the article

of permanent disorders of the development of movement and posture, causing activity limitations that are attributed to non-progressive disturbances that occurred in the developing foetal or infant brain." Rosenbaum et al. added, "The motor disorders of CP are often accompanied by disturbances of sensation, perception, cognition, communication, behaviour, by epilepsy and by secondary musculoskeletal problems." [12]. While this remains a widely used definition, challenges remain around the heterogeneity of presentation, the interpretation of the term 'non-progressive disturbances' and the age at which cerebral palsy can be acquired. While the etiologies of CP are many, abnormal neuroimaging findings are seen in between 80 and 90% of children with CP [13–15], with changes in neuroimaging broadly linked to different presentations. There is not a singular diagnostic test for CP; however, a combination of early cranial Magnetic Resonance Imaging (MRI), together with the Hammersmith Infant Neurological Examination and General Movements assessment, has a 97% sensitivity to detection of high CP risk before the age of 6 months [16].

Individuals with CP have variable motor impairments, topographical involvement, and levels of functional ability. Classification of the motor impairment has historically been based on the description of the movement and posture disorder and the limbs affected. Two main movement disorders are described: pyramidal (spastic CP) and extrapyramidal (ataxic, athetoid or dystonic CP). Spasticity is defined inconsistently in the literature, but based on the SPASM Consortium definition, broadly includes "disordered sensori-motor control, resulting from an upper motor neuron lesion, presenting as intermittent or sustained involuntary activation of muscles" [17], or "all intermittent or sustained involuntary hyperactivity of a skeletal muscle associated with lesions of the descending motor pathways" [18]. Bar-On et al. [19] have offered that a quantitative and specific definition of spasticity is important, suggesting a return to the classical Lance definition [20] of "a velocity dependent increase in stretch reflex" with renewed emphasis on techniques for specifically measuring this aspect of hypertonicity. Contribution to this debate is outside of the scope of the present article, but we note that there is increasing convergence on a common definition by both researchers and clinical practitioners.

Classification in CP uses different descriptors and may assess different aspects of the clinical manifestation such as topography of affected limbs, severity of movement impairment, or upper limb manual ability. For instance, regarding topographical classification, unilateral involvement of an arm and leg is termed hemiplegia, predominant lower limb involvement is termed diplegia, and involvement of all limbs is termed quadriplegia [5, 21]. While historically widely used, this topographical classification system has low reliability and validity across observers [22] and arguments have been made for its phasing out due to imprecision of description [23]. The Surveillance of Cerebral Palsy in Europe (SCPE) classification divides the movement impairment in CP into spastic, dyskinetic and ataxic forms, with involvement of either one (unilateral) or both (bilateral) sides, and has been shown to have higher reliability when standardised data collection forms are used to guide the reviewer [24, 25]. The Gross Motor Function Classification System (GMFCS) [26] is graded from levels I to V and describes usual gross motor function. The GMFCS uses descriptors at each level defining motor abilities applicable to each level. Children who function at GMFCS level I are independently ambulatory across all surfaces with difficulties only with coordination and balance. Conversely, children who function at GMFCS level V lack head control and require support with all tasks of daily living. Overall, approximately 60% of children with CP are independently ambulatory (GMFCS levels I to II), 11% use some form of walking aides (GMFCS level III), and 29% are predominantly wheelchair users (GMFCS levels IV and V) [27]. Similarly, other common functional classification systems such as the the Manual Ability Classification System (MACS), the Communication Function Classification System (CFCS), and the Eating and Drinking Ability Classification System (EDACS) also provide reliable classifcations (also scaled by levels I-V) of the functional abilities of individuals with CP [28].

Motor development and musculoskeletal growth in typically developing infants and infants with cerebral palsy

Limb movements are largely involuntary before three months of age and occur with other movements of the body. These 'general movements' – movements in which all of the body participates – gradually give way to goal-directed arm and leg movements by 3 to 5 months of age, with control being attained centrally (e.g. arms) before peripherally (e.g. hands) [29]. Conversely in the infant with CP, achievement of motor milestones is delayed and general movements that are reduced in complexity and variation are seen in the first few months of life [30]. Typically developing (TD) muscle growth has not been mapped over time in infants but, by 15 months of age, children with CP have medial gastrocnemius muscles that are already smaller than those of their peers, a finding more evident in those children who are least mobile [31]. This reduction in growth, due to smaller width of muscle fibres, suggests that early typical levels of neural activity and physical activity are critical for normal infant muscle growth. Consistent with this hypothesis, animal

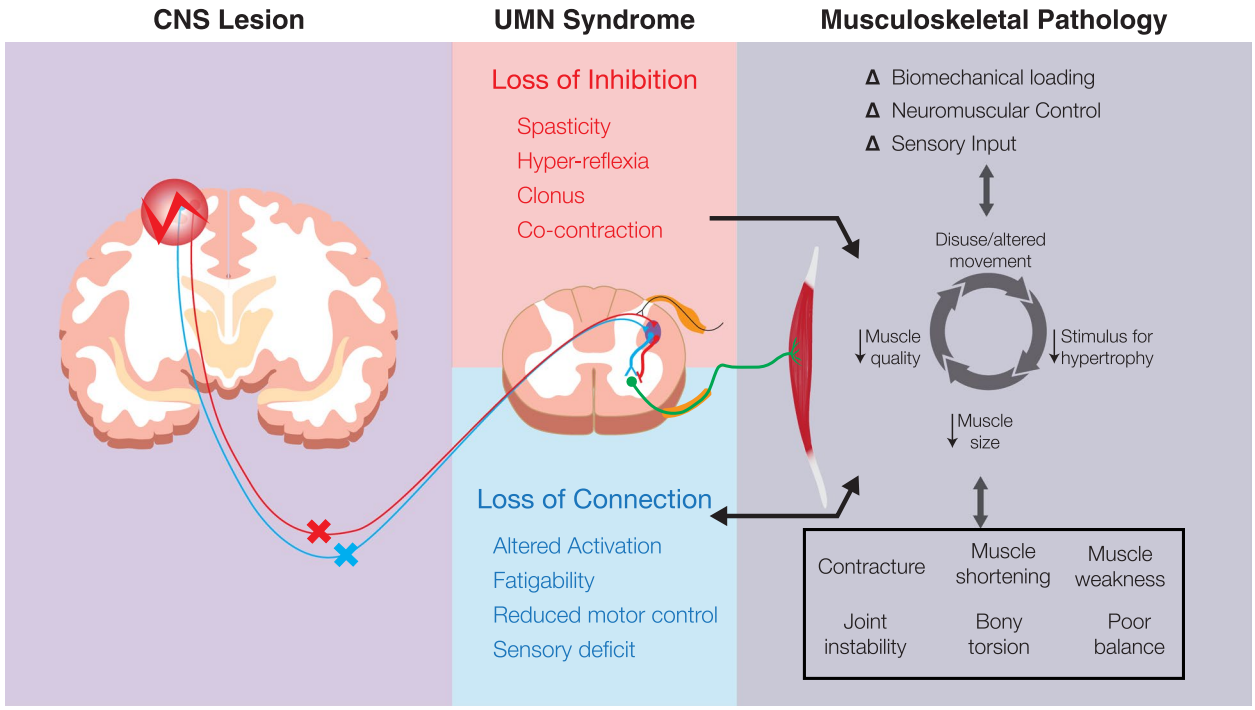

Fig. 1 Cerebral Palsy is caused by a lesion in the developing brain, which causes downstream neuromuscular effects. Musculoskeletal effects of CP worsen progressively over time, even though the neural lesion is static. The musculoskeletal pathology may progress in a vicious cycle, where e.g. diminished loading promotes muscle weakness, which further promotes diminished loading. Here we represent both loss of inhibition and loss of connection, and propose that debate and discussion is warranted on the influence that each of these has on the clinical manifestation of CP. Figure our own, created using Adobe Illustrator (Adobe, Inc., San Jose, CA, USA) under the University of Auckland site license

models of brachial plexus palsy have shown that division of upper plexus in neonatal rats rapidly leads to reduced cross-sectional and longitudinal growth of C5/C6 innervated muscles with increased fibrosis, fat infiltration, and shoulder or elbow contracture development [32]. While a specific animal model of CP that recapitulates the motor phenotype remains elusive, it is likely that these results from brachial plexus palsy animal models will also apply to CP.

As the child with CP ages, further reduction in muscle growth in involved limbs leads to muscles in adulthood that are smaller, shorter, and weaker, with reduced exercise tolerance and greater fatigue [33–37]. These features are additive to the neurologic impairments in CP, which include hypertonia, hyperkinesis and altered motor control [38, 39] (Fig. 1). Joint and muscle range of motion (ROM) can become increasingly limited over time, and secondary muscle and joint contractures develop, resulting in pain, hip subluxations, and scoliosis [38, 40]. Altered musculoskeletal function becomes evident early in life and typically worsens over time, greatly impacting the lives of individuals with CP across their lifespan [41]. The role of musculoskeletal growth in CP is under-studied; the effects of muscles and bones that are growing, in conjunction with neural impairments and altered mechanics, may explain some of the progression of symptoms in CP. Beyond this, the link between the neural insult and the cellular myopathies of cerebral palsy is unclear, but there may be a central mechanism describing how cellular muscular components are altered by the neural lesion in CP. These questions are ripe for further work. Broadly, optimisation of muscle health in CP requires an understanding of the complexities of muscle morphology and dynamics, and warrant an elucidation of the effects of the pathology on the musculoskeletal system, which in turn play a significant role in the manifestation of CP.

This focused narrative review provides an overview of recent literature on the effects of cerebral palsy on muscle growth and development and how this influences the progression of cerebral palsy and impacts the lives of those with this condition. We present current descriptions of the musculoskeletal aspects of cerebral palsy, focusing primarily on skeletal muscle, and assessing size scales from the whole patient down to the cellular level. We focus attention on the role of musculoskeletal growth, and how this may interact with other aspects of CP to progress symptoms over time.

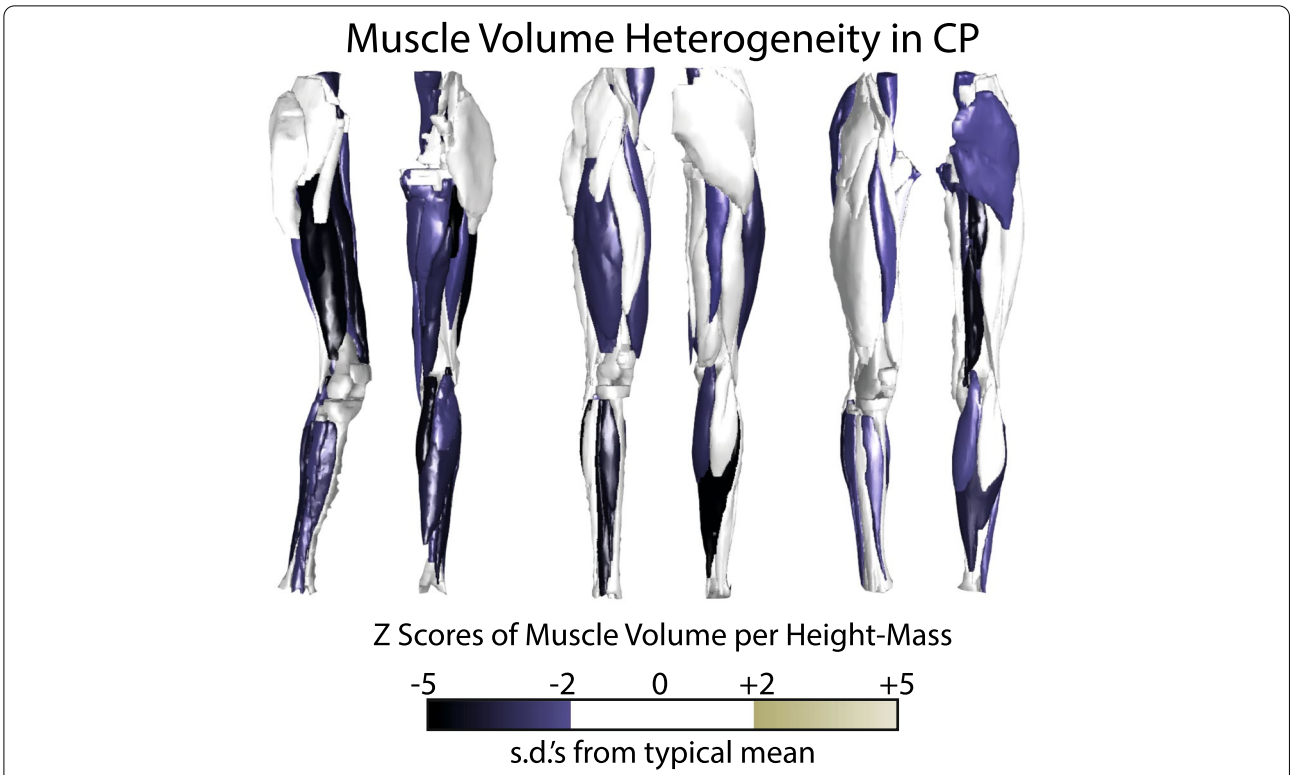

Fig. 2 Z-scores of height-mass normalized muscle volumes reveal the heterogeneity of muscle size deficits in CP. Volume deficits are non-uniform within limbs, and muscle deficit profiles are non-uniform across individuals with CP, emphasizing the importance of evaluating the pathology on a patient-specific and muscle specific basis. Figure redrawn with permission from Handsfield et al .[49], using Adobe Illustrator (Adobe, Inc., San Jose, CA, USA) under the University of Auckland site license

Effects of cerebral palsy on muscle size and architecture

Muscle size and architecture are measurable features at the macro- and meso-scale that govern a muscle's functional capacity [42]. Deficits to muscle size and architecture indicate functional loss. As a result, previous work has used medical imaging to investigate differences in size and architecture between typical and CP groups [41, 43–51]. Common findings include deficits in muscle volume and cross-sectional area [41, 43–50], and overstretched sarcomeres [42, 52, 53]. Here, we review this literature and propose that these changes to muscle may result from dysfunctional growth at the cellular level which limits potential increases in physiological cross-sectional area that may otherwise occur in response to aging and mechanical stimulation of exercise on the muscle; dysfunctional cellular growth may also limit serial sarcomerogenesis for reasons that, at present, remain hypothetical.

Muscle size

Muscle volume represents gross size and can be determined from medical imaging. Geometrically, muscle volume is the three-dimensional representation of muscle length and cross-sectional area, or thickness in sagittal and coronal planes. Given that all three measures may be reduced in muscles from individuals with CP, it is unsurprising that muscle volume is markedly reduced compared to TD muscles [41, 43–49]. Percent differences in volumes vary widely across individuals and muscles but may be as much as 43% reduced [47, 49]. While individuals with CP are often smaller in height and mass than TD individuals, small volumes are not explained by the smaller statures of individuals with CP [49]. Current data suggests that the greatest reductions are associated with reduced overall function according to GMFCS levels [54, 55].

Another aspect of muscle size in CP is the heterogeneity of expression of volume deficits (Fig. 2) [49, 56]. In a study of 35 lower limb muscles in 18 adolescents, Handsfield et al. demonstrated that muscles were not uniformly reduced in volume in individuals with CP, implying that not all muscles are affected equally by the neurologic condition [49]. The profile of muscle sizes was also significantly different between individuals with CP, implying a unique manifestation for each individual. In light of

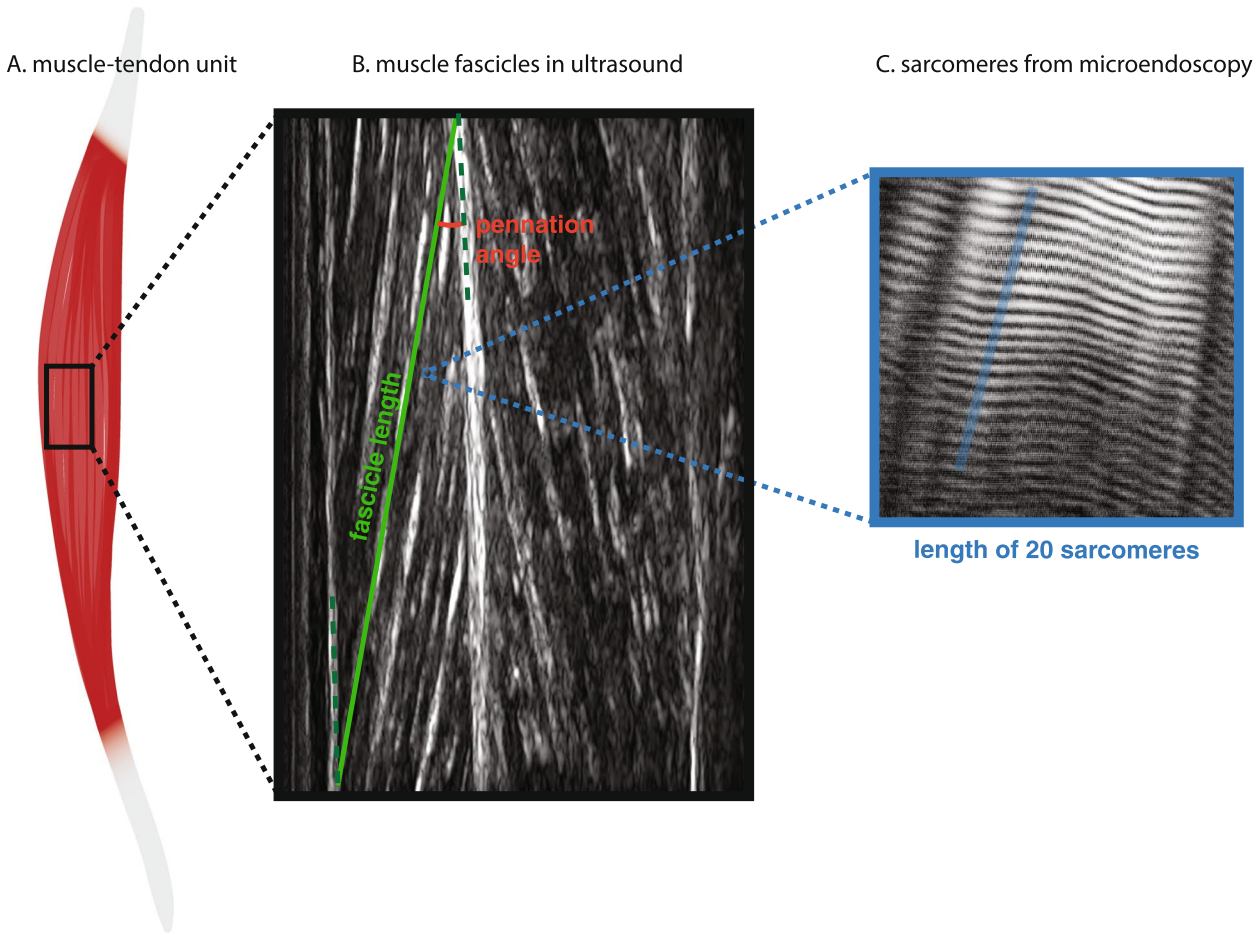

Fig. 3 CP affects muscle structure at the level of the muscle-tendon unit (**A**), the fascicles (**B**), and sarcomeres (**C**). **A**: Muscle belly lengths have been observed as shorter in CP, while tendons have been reported as longer. **B**: Fascicle lengths (green line) are reported to be shorter or similar in length between individuals with CP and TD cohorts, while pennation angles (red) are reported as similar or smaller in individuals with CP, sometimes with joint angle dependencies. **C**: microendoscopy image shows a muscle fibre and sarcomere striation pattern, blue line captures ~20 sarcomeres in series, reported to be longer in individuals with CP. Figure our own, created using Adobe Illustrator (Adobe, Inc., San Jose, CA, USA) under the University of Auckland site license

this, it should not be surprising that there are between-study differences in volume or length deficits reported, e.g. soleus volumes reported in Oberhofer et al. [45] vs Handsfield et al. [49]. Differences between studies such as these are a feature of CP and reinforce the importance of treating CP subject-specifically [56].

Muscle-tendon length, sarcomere length, and Pennation angle

The muscle-tendon unit (MTU) (Fig. 3) comprises the muscle belly and the tendons. Compared to typical muscles, affected muscle bellies in CP are generally shorter, smaller in thickness and cross-section, and have longer tendons [41, 49, 50]. Overall, the MTU of affected muscles are likely shorter in CP muscles at the point of passive-force generation, although this is muscle- and patient-specific, and varies with age and severity of CP.

Ultrasound studies on plantarflexor muscles have shown similarity between typical cohorts and cohorts with CP for both muscle belly length and fascicle length[1] (Fig. 3) [44, 57–59] or alternatively shorter in muscles from individuals with CP [60]. Using diffusion tensor imaging, Sahrmann et al. [50] showed no significant differences in soleus muscle fascicle lengths between a group of typical adolescents and a group with CP;

[1] The fascicle length of a muscle is defined here as the length of the muscle in the direction of the muscle fibres or fascicles. We refrain from the term *fibre length* as fibres themselves terminate intrafascicularly; the term *fascicle length* better represents the functional length of a muscle measured from origin to insertion along the fibre direction.

D'Souza et al. [51] showed significantly shorter fascicles in medial gastrocnemius muscles from individuals with CP compared to typical. Across imaging modalities, fascicle length differences range from no difference [46, 50, 61] to up to 25% shorter in muscles from individuals with CP [60, 62] or in some cases beyond 40% [63].

At the micro-scale, the fundamental unit of muscle is the sarcomere (Fig. 3). Human muscle fibres are composed of tens of thousands of sarcomeres in series [64, 65]. A muscle's functional ROM is affected by the number of sarcomeres in series, with fewer sarcomeres contributing to a smaller overall muscle excursion. It is difficult to know the resting length or number of sarcomeres in individual muscles without direct investigation. Intraoperative methods to determine sarcomere lengths [42, 66] have reported generally consistent findings that sarcomeres from muscles of individuals with CP are significantly longer and fewer in number than in TD muscle. However, previous studies either lacked a consistent control group [52, 67] or measurements were made at a prescribed joint angle where passive tension may have been different between groups [42, 53]. Furthermore, indirect measures of the forces generated by muscle at different lengths [68–71], have suggested similarity in sarcomere force-length relationships between groups with CP and TD groups. Despite these discrepancies, direct evidence seems to suggest that CP is associated with fewer sarcomeres in series and longer sarcomere lengths relative to fascicle length (Fig. 3), which conceivably plays some role in muscle contracture. Novel methods to assess sarcomere length in vivo, for example microendoscopy [64, 72, 73], used in conjunction with macro-level imaging, such as ultrasound or diffusion tensor MRI, may provide greater understanding of muscle fibre level adaptations in CP.

Tendon, aponeurosis and other connective tissue also play a role in the generation of passive tension in the MTUs. Tendons in the lower limb of individuals with CP have been observed to be on the order of 10% longer than TD controls [71, 74, 75], which may be a compensation to shortened muscle bellies. However, increased tendon lengths appear insufficient to fully compensate for the shorter fascicle lengths, thus leaving stretched sarcomeres and a muscle which is overall tighter and less extensible than typical [76–78]. In other populations where atrophy is known to occur, e.g. ageing muscle, tendinous tissues are presumed to adapt to allow a normal ROM [79]. There is currently little understanding around how tendinous tissue adapts in individuals with CP and whether this allows more optimal force generation at shorter overall MTU lengths.

A muscle's pennation angle is defined as the angle between the muscle fibre direction and the external tendon direction (see Fig. 3). Studies using ultrasound and diffusion tensor MRI have explored pennation angles in muscles from individuals with hemiplegic and diplegic CP and from typical controls. Results have been mixed with reports of increases [60, 80, 81], decreases [57], and no significant differences [50, 51, 62, 74, 82]. It should not be surprising that results vary on this question given the general heterogeneity of CP pathology across both muscles and individuals [49]. Diminished pennation angles have been associated with sarcopenia and atrophy [83–85], although in individuals with CP this may be complicated by altered sarcomere numbers and tendon lengths. Some of the aforementioned studies found a dependency on joint position [57, 76], suggesting a difference in resting joint angle that is consistent with an overall tighter MTU in CP.

Muscle physiological cross sectional area

Physiological cross sectional area (PCSA) is the cross-sectional area perpendicular to muscle fibre direction when the muscle is at optimal sarcomere length. For typical individuals, PCSA is a proxy for maximum isometric force [86]. Because PCSA is tightly linked to force production, it is an important measurement for understanding strength deficits in CP, bearing in mind that muscle quality, i.e. specific tension, may also be impaired in individuals with CP [55, 87–90]. Previous authors have used muscle thickness and anatomical cross-sectional areas as indicators of PCSA, largely reporting deficits among individuals with CP [31, 62]. Two recent studies using diffusion tensor MRI showed reductions in cross-sections of around 40% in the soleus [50] and 10% in the gastrocnemius [51] in individuals with CP compared to TD. Neither of these groups determined sarcomere lengths as part of their study. Because muscles are isovolumetric when they stretch and contract, CP muscles with 20% longer sarcomeres would also be 20% smaller in cross-section at that position. Thus, some of the reduction in observed PCSA could be accounted for by overly long sarcomeres in CP (Fig. 4). Studies involving concomitant fascicle length assessment and sarcomere length determination are an important future work to resolve this question. It is possible however that sarcomere length increases do not fully account for observed reductions in muscle cross-sections, indicating structural muscle weakness as a feature of CP. Continued work is warranted to connect sarcomere lengths, fascicle lengths at neutral joint positions, and PCSA in CP and TD populations.

In summary, CP is associated with muscles that may or may not be shorter in fascicle length compared to typical; the limited evidence on sarcomere lengths suggests that there are fewer sarcomeres in series that are stretched out in muscles from individuals with CP (Fig. 4); and

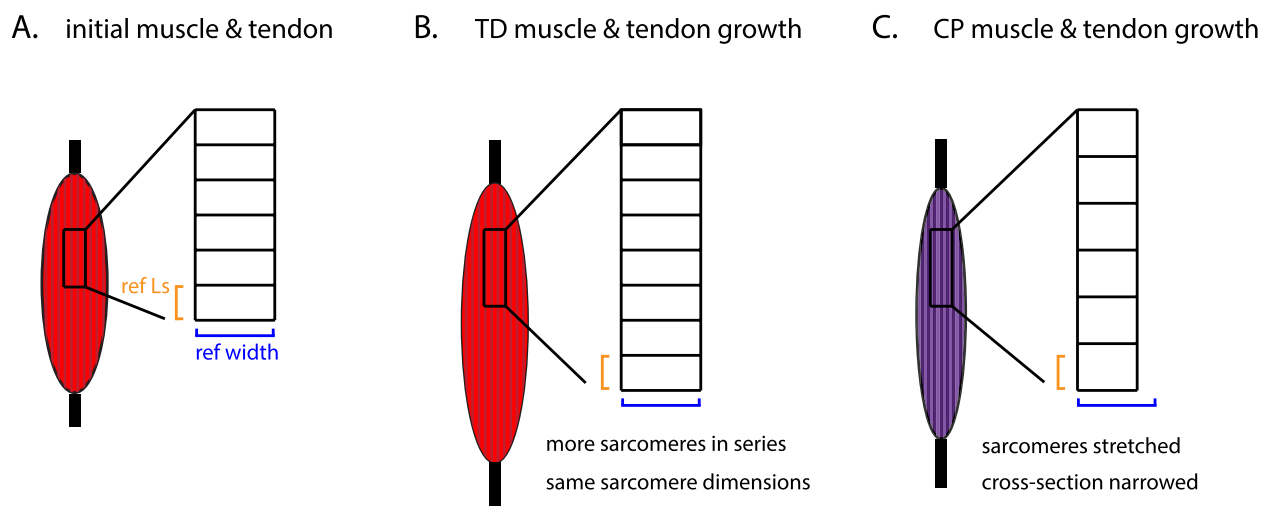

Fig. 4 Hypothetical mechanism for increased sarcomere length and reduced apparent PCSA in CP muscle (inset represents sarcomere structures within muscles). A typical muscle grows in length by adding sarcomeres in series (**A** and **B**). Sarcomere length at a neutral joint angle (Ls) remains constant but the number of sarcomeres in series increases. In individuals with CP, muscles and tendons also lengthen with growth, but sarcomeres stretch out, rather than adding in series, while tendons lengthen (**A** and **C**). This effect may contribute to reduced cross-sections (see ref. width in **C**); a muscle with 20% longer sarcomeres is 20% narrower in cross-section because of the isovolumetric property of muscle. Figure our own, created using Adobe Illustrator (Adobe, Inc., San Jose, CA, USA) under the University of Auckland site license

reduced thicknesses and cross-sectional areas indicate an impaired strength capacity among individuals with CP. These changes may be accompanied by longer tendons. What remains unclear is whether smaller muscles are the result of a process of atrophy or a lack of growth. Atrophy implies that the muscles are becoming smaller over time, while lack of growth suggests that the muscles are failing to develop adequately alongside a growing body. One mechanism linking these observations concerns the lengthening of bones in growing children and adolescents. The process of bone lengthening by growth will mechanically lengthen the muscles and tendons. In TD children, muscles respond by adding sarcomeres in series and growing in length (Fig. 4). If CP is associated with a failure of muscles to add sarcomeres in series, the muscles accommodate the growing skeleton via overstretched sarcomeres and tendons (Fig. 4). An alternative explanation is that fascicle excursion is restricted by a stiffer extracellular matrix [53] and restricted motion then inhibits longitudinal growth of the muscle. There is strong evidence that muscle growth is impaired in CP for both longitudinal growth (addition of sarcomeres in series) [51, 53, 91] and cross-sectional growth (increases in PCSA) [49–51]. Other musculoskeletal effects of CP, e.g. longer tendons, may be explained as consequences of these more primary causes. We propose that the impaired capacity for growth in CP manifests at the cellular level, a hypothesis that will be discussed in detail in the next section. The link between the neural lesion and the altered cellular environment remains elusive, but is an important area for further directed study.

Muscle cellular physiology and growth

The cellular environment and morphology of skeletal muscle is altered in CP compared to typical [92]. Common histological observations of muscles from individuals with CP include altered fibre type distribution, increased variability in fibre size, rounding of muscle fibre cross-sections [93, 94], increased lipid composition [94–96], and excess connective tissue [53, 95, 96]. These pathological changes are linked to reduced regenerative potential and have been correlated with changes in pro-inflammatory cytokines, satellite cell concentration, and fibroblast activity, all of which are important for achieving muscle homeostasis following mechanical damage to muscle [95, 97–99]. The process of muscle regeneration and growth is the subject of ongoing research, but can be summarised by the inter-dependent processes of (1) mechanical injury; (2) inflammation marked by the clearance of necrotic tissue by myeloid cells; (3) repair marked by satellite cell activation and differentiation into myoblasts and myocytes, which fuse to repair or generate muscle cells; and (4) remodelling of the extracellular matrix (ECM) by fibroblasts (Fig. 5).

Aberrant changes in levels of cytokines have far-reaching effects on the whole muscle as a result of altered regeneration. Elevated levels of pro-inflammatory cytokines interleukin-6 (IL-6), tumor necrosis

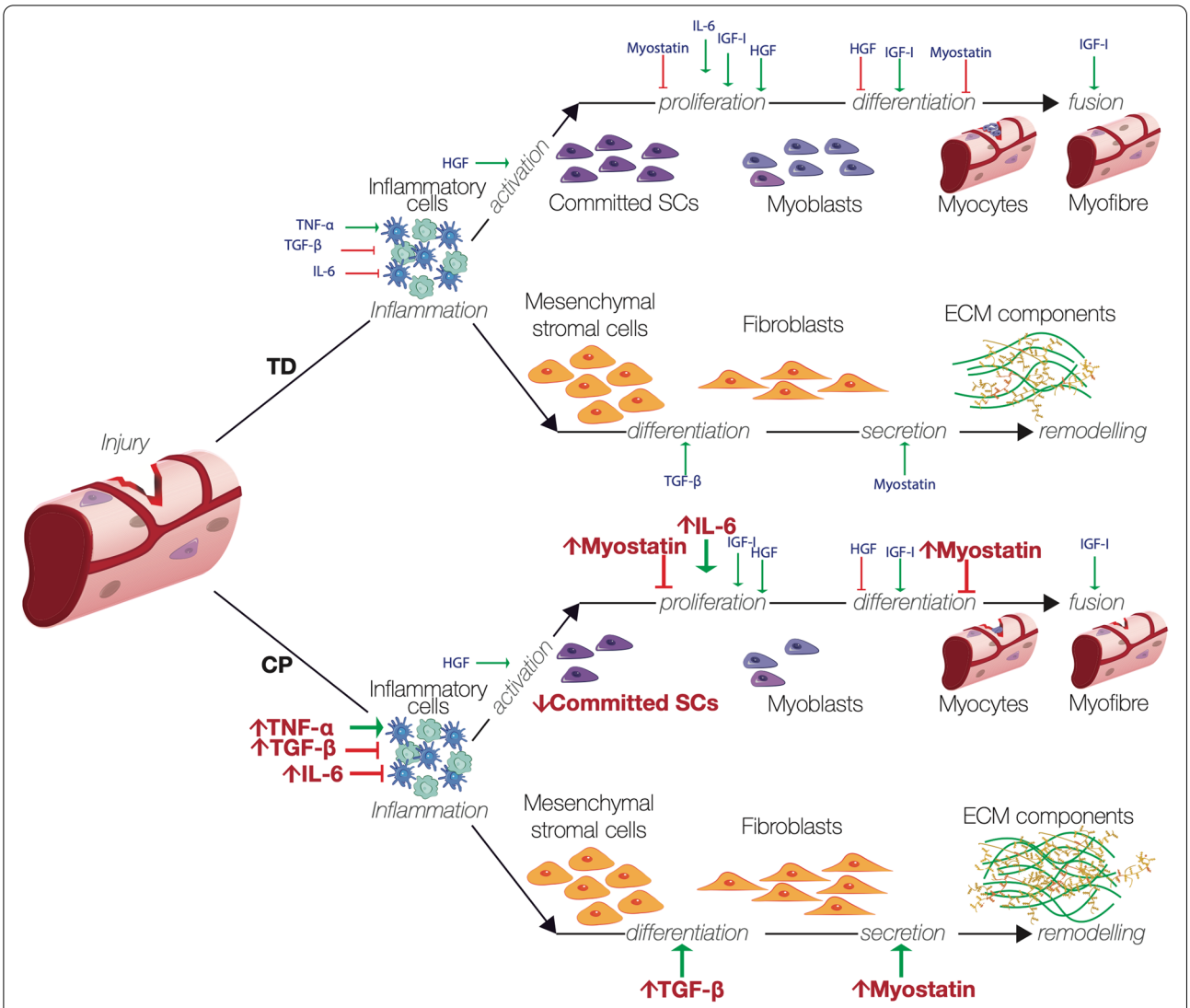

Fig. 5 Mechanical injury is the first step in muscle regeneration and growth and initiates a cascade of cellular and molecular events in skeletal muscle. Inflammatory cells debride tissue and clear damaged muscle cells. Release of appropriate cytokines activates resident satellite cells to repair the fibre while fibroblasts remodel the ECM. CP muscle displays increased expression of TNF-a, TGF-B, IL-6 and myostatin, and fewer SCs. Increases in fibroblast activity result in smaller fibres and excess ECM. Figure by Stephanie Khuu/ CC BY 4.0

factor alpha (TNF-α) have been found in muscles from individuals with CP and are linked to reductions in protein synthesis, stunted growth, and muscle atrophy [95]. Transforming growth factor beta (TGF-ß) is elevated in CP muscles compared to typical, as is myostatin, a negative regulator of skeletal muscle mass and promoter of protein degradation [95, 100]. Myostatin is up-regulated by increased expression of TGF-ß, and impairs satellite cell proliferation during growth and repair of skeletal muscle by signalling quiescence of satellite cells [101–104] while simultaneously enhancing fibroblast and ECM protein proliferation [105].

Satellite cells (SCs) are resident stem cells considered to be the primary agents of repair in skeletal muscle. Reductions in SC concentration of 40–70% have been reported for muscles from individuals with CP compared to typical [91, 95]. In addition to a loss of SCs in CP muscle, the regenerative ability of remaining SCs may be compromised. Cultured myoblasts derived from SCs from individuals with CP show down-regulated markers of differentiation and an ~ 85% decrease in the rate of fusion and myotube formation [97]. The decrease in both concentration and efficacy of SCs contributes to a diminished regenerative potential in the muscle environment

in CP. However, the mechanistic role of SCs in growth and repair of CP musculature is not well understood. For instance, it may be that SCs are more pertinent to hypertrophy in young muscle for growth and repair, rather than in older individuals; the role of SCs in regulating fibroblast activity during collagen production and ECM remodelling needs further exploration [98, 99].

Healthy muscle regeneration and ECM remodelling are enabled by the reciprocal interactions between SCs and fibroblasts and their related rates of proliferation [106]. ECM is the non-cellular, endomysial connective tissue that surrounds muscle structures [107, 108]. ECM is created and repaired by fibroblasts which secrete ECM components, including collagen [109]. Different ECM compositions have been observed in individuals with and without CP and may account for both loss of function and loss of regenerative potential observed in CP. In connective tissue staining of human flexor carpi ulnaris muscle fibre bundles, tertiary perimyseal collagen was three-fold higher in CP compared to control samples [93]. Moreover, hamstring muscles from children with CP had increased Collagen I and laminin between fibres, indicative of excess connective tissue [53]. Booth et al. found that the level of collagen accumulation in muscle biopsy samples from children with CP was significantly correlated with the Modified Ashworth Scale [110], indicating a link between excessive connective tissue and contractures in CP. On a transcriptional level, CP muscle has increased gene expression for collagen production and pro-inflammatory cytokines compared to TD, both of which can lead to aberrant ECM expansion [95].

Optimal repair of muscle is associated with initial construction of an ECM scaffold, followed by feedback mechanisms to ensure the resolution of fibrosis [111]. When feedback mechanisms are compromised or when injury is repetitive, excess collagen deposition by fibroblasts results in scar tissue formation and loss of contractile function in the area [112]. In cases of spasticity and contractures, it is common to observe increased ECM, fibrosis, and fatty infiltration into muscle [93, 110, 113]. The precise cellular mechanisms for each change remain unknown, but it is thought that increased ECM and fat content may act as a structural barrier to normal growth in CP. Further work is needed on the relationship between muscle components at the cellular level, deposition of structures during muscle and ECM repair following damage, and growth mechanics in CP. An elusive but worthwhile goal for future research is uncovering mechanisms linking the principal neural insult in CP with the commonly observed cellular myopathies—reduced satellite cell number, fibrosis, and reduced muscle fibre area fraction. The elucidation of a neural or neuromuscular antecedent of these myopathies would represent a huge leap forward in understanding and treating spastic CP. In this respect, it is worth considering that CP generally expresses subject-specifically and the field may uncover several unique mechanisms at the neural and cellular scale that individually or collectively contribute to an individual's specific expression of muscular development.

Biomechanical loading and growth of muscles in CP across the lifespan

Altered muscle morphology and growth in individuals with CP have biomechanical consequences, which then affect morphology and growth in a cyclical fashion. For example, painful or tiring gait may result in a reduction in voluntary physical activity, which inhibits biomechanical loading to a level that inhibits hypertrophy and results in smaller muscles, further making movement painful or tiring. The cyclical feedback between mechanics, structure, and growth exists at multiple levels and has consequences across the lifespan.

While research is lacking on how morphology and mechanics change over time in individuals with CP compared to typical, piecing together a series of cross-sectional studies and short longitudinal studies suggests muscle growth is impaired from an early age in individuals with CP [114]. Typically within the first years of life, the human body experiences rapid growth in both muscle length and cross-sectional area, enabling attainment and mastery of functional tasks. In individuals with CP, reduced muscle volumes may begin early in childhood. Cross-sectional studies investigating volume of the medial gastrocnemius muscle in infants with CP [31, 115] supports the concept that early growth rate is reduced compared with TD controls [76]. Herskind et al. [31] and Willerslev-Olsen et al. [115] provide evidence that at 12–15 months of age the muscle volume of infants with CP is already reduced compared to TD children. Given that developmental milestones such as standing and walking occur at this age, it may be that the earliest musculoskeletal aspects of CP set the stage for subsequent impaired movements over the lifespan.

The trajectory of typically developing muscle size and strength steadily increases before reaching a peak in the early to mid-20s [115]. Fitness activities aim to promote development of muscle health during this time and maintain health above the functional strength threshold to combat effects of aging and sarcopenia. Individuals with CP participate in significantly lower rates of physical activity than their TD counterparts [116–121] and entertain fewer opportunities for mechanical loading. This effect increases with decreasing function, according to GMFCS levels [122], potentially contributing to a vicious cycle of 'disuse' and secondary sarcopenia, as discussed by Verschuren et al. [37]. Trajectories of muscle

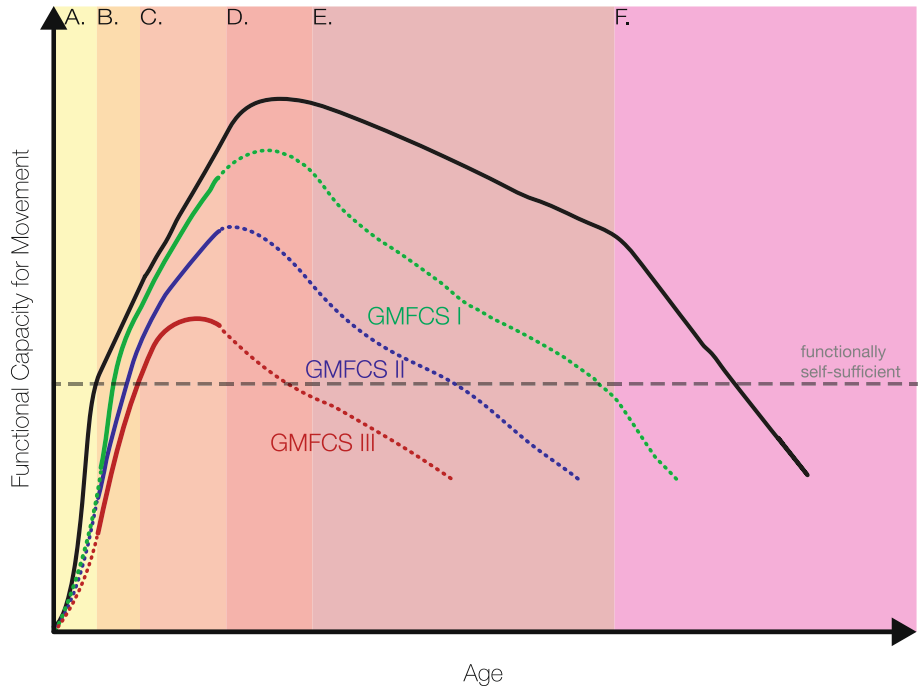

Fig. 6 Hypothetical trajectory of muscle function (y axis) across the lifespan (age, x axis) in healthy TD individuals and individuals with CP, plotted for GMFCS level I, II, and III, an expansion of the concept proposed by Shortland [114]. Proposed trajectories transition from solid to dashed lines where literature is sparse. We do not present GMFCS IV-V—a reflection of the dearth of data from these cohorts. The dashed horizontal line represents the hypothetical threshold for functional self-sufficiency. Shaded blocks represent life stages to mark variations in growth rates: **A**) Infancy-early childhood: a period of rapid development, **B**) Childhood: a period of continued improvement, **C**) Adolescence: protracted improvement in TD with lesser gains in CP, **D**) Early-adulthood: reaching our peak, **E**) Adulthood: gradual decline **F**) Older age: rapid decline. Figure our own, created using Adobe Illustrator (Adobe, Inc., San Jose, CA, USA) under the University of Auckland site license

volume over time for individuals with CP reaches a lower peak and peaks earlier in life, and is nearer the functional threshold throughout the lifespan (Fig. 6).

Rapid declines in function in otherwise healthy typical individuals is generally expected around the seventh or eighth decade of age [115]. This decline is proposed to occur much earlier in individuals with CP, due to the combined effects of contractures, altered neural drive, reduced mechanical loading, and sub-optimal nutrition [114, 123]. In addition to lower than typical function [124, 125], significant functional declines have also been reported in adolescents and adults with CP [126, 127]. For instance, 31–35% of adults with CP experience a decline in walking ability before the age of 35 [128, 129]. Longitudinal studies support this, finding that walking ability declines with age and are more rapid among individuals with less functional capacity at onset of adulthood [130, 131]. Deterioration in walking function seems to be related to increased pain and fatigue as well as reduced balance [131]. Deficits to neural control, muscle weakness, joint contracture, and spasticity likely interact with the natural progression of ageing to limit functional capacity and physical activity [132]. There is a disappointing lack of research on adults with CP, and even more so in terms of the longitudinal changes of muscle. Interventions and management aimed at improving and maintaining muscle health across the lifespan need to be applicable to all individuals with CP, but perhaps even more so in individuals known to have limited biomechanical loading who are at risk of secondary sarcopenia.

Consideration of biomechanical loading in CP is important in light of early deficits experienced with this pathology and the narrower functional time across the lifespan. Our understanding of cellular physiology and growth in CP is still limited, but coupling this with our understanding of biomechanics at multiple scales may help develop future strategies for maximizing opportunities for muscle growth and development across the lifespan in individuals with CP.

Impacts to muscles of common treatments for CP

Much of our understanding of muscle in CP is absent knowledge of the natural untreated progression of muscle in CP. Participants with CP involved in research studies have typically been treated with sequential interventions

and management approaches, which confound reductionist investigations to fully understand the longterm impacts of the treatments. Here we discuss potential effects of treatment strategies on muscle size and quality.

Pharmacological agents and surgical procedures are frequently used for tone management in CP, including Botulinum Neurotoxin A and selective dorsal rhizotomy [133]. Botulinum Neurotoxin A (BoNT-A) injections reduce spasticity with small but variable effects on functional abilities [134, 135]. Recent concerns have emerged that BoNT-A may contribute to muscle atrophy and fibrosis, effects that may outweigh the positive short term reduction in spasticity [136]. Studies investigating echo intensity—a proxy for fatty infiltration—and muscle volume following BoNT-A injection suggests increased fat and decreased muscle volume [55, 88, 137, 138]. However, BoNT-A may not have as profound effects in humans as was previously reported in animal studies [137], and BoNT-A injected muscles are not precluded from also experiencing hypertrophic and functional strength gains following strength-training intervention [139]. Further, BoNT-A does not appear to affect agonist muscles in close proximity to the injected muscle, which may undergo compensatory hypertrophy [138, 139]. However, it bears considering that the chemodenervation of muscle associated with BoNT-A has been linked to acute atrophy in both animal studies [140, 141], and humans [137, 138, 142, 143]. Beyond this, it should be acknowledged that the long-term effects of BoNT-A remain under-studied, and continued research and some clinical caution are thus appropriate [144, 145].

Selective dorsal rhizotomy (SDR) is a neurosurgical procedure whereby selective sensory nerves running through the spine are irreversibly severed, with the intent to decrease the sensory input of the overactive spastic muscles [146]. The procedure is widely regarded to alleviate muscle tone in the lower limbs of children with spastic diplegia [147–149], and when combined with physiotherapy lead to improvements in gross motor function [147, 150], pain [151], and functional independence [147]. However, researchers highlight the critical importance of careful patient selection to avoid detrimental outcomes of the procedure (i.e. patients with dyskinesia or ataxia and without adequate muscle strength [147, 152]). Other than a reduction in tone, the impact on variables of muscle are under-studied, and evidence on outcomes are still limited to short-term studies.

Muscle-tendon lengthening surgeries are a common muscle surgical intervention for children with CP, with the aim of restoring joint range of motion and normalising gait [153]. Potentially as a result of serial sarcomere loss following surgery, reductions in muscle fibre length and increased deep fascicular-aponeurosis angles have been measured post-surgery [61], as have reductions in muscle belly length [154]. Yet parallel improvements in joint range of motion imply an overall lengthening of the musculotendinous unit, with an increase in tendon length [155]. Though atrophy of the muscle might be expected in the short-term following surgery, middle-term findings are mixed [154, 155], but indicate a recovery and continued increase after such surgery. In contrast, muscle belly length appears to remain reduced relative to bone length; more work is needed in this area to determine the specific impacts of lengthening surgeries on the muscle belly and tendon separately [154, 155].

Treatment strategies for muscle contractures vary in scope and effectiveness. Passive stretching is generally not regarded as useful in contracture prevention or management [156]. Prolonged stretching of MTU components via orthoses or casting may improve joint ROM, but may weaken muscles or adversely affect the muscle belly tendon length ratio [157]. Prolonged use of Ankle-Foot Orthosis may not prevent worsening of a contracture [158]. Studies on bracing have shown increased ROM without increasing muscle belly length via increased tendon extensibility but also reduced muscle volume [159].

Therapeutic interventions targeting muscle weakness and motor control/ neural activation in CP include strength training, mobility training, and functional electrical stimulation. Strength training has successfully induced improvements in muscle volume [139, 160], fascicle length [58], cross-sectional area [58], and muscle thickness [58], while studies employing neuromuscular electrical stimulation have shown improvements in cross-sectional area [161, 162], muscle thickness [162], and muscle volume [163, 164]. It should be noted that gains in muscle architecture and strength may not translate to functional improvements such as walking speed or gross motor function [165, 166]. It is broadly recognized that muscles tend to be weak in cerebral palsy; for this reason, strength training should not be categorically ruled out, but consideration should be put towards the interventions themselves and whether the activities are directed at achieving a desired outcome or functional movement for the patient [167]. In a systematic review of 166 studies, Novak et al. found aerobic fitness training to offer an overall positive effect in CP, in general, but found equivocal results for strength training based on the lack of connection to functional gains [168]; however, in a follow-up review, strength training was found to be a positive intervention in certain contexts (e.g. after casting) and a weak positive to promote fitness, physical activity, and quality of life in general [133]. Novak et al. also reported equivocal results for electrical stimulation [133, 168].

Considering this, we add our support of the principle that targeting muscle weakness may be the most beneficial when there is a focus on therapies that also train motor control and promote a functionally useful movement, such as gait training [166, 169], while also involving mechanical loading.

Conclusions

Skeletal muscle in CP is associated with observable deficits at several size scales, including reduced muscle volumes, fascicle lengths, and pennation angles, stretched tendons, and fewer sarcomeres in series that are stretched out. Impairments to muscles are heterogeneous in CP and deficits tend to vary across muscles and individuals. Impaired growth in CP is thought to commence at an early age and may relate to deficient concentrations and effectiveness of satellite cells. Higher proportions of ECM and sometimes fatty infiltration are seen in CP, which may be related to altered SC concentrations as well as the dynamic interactions of fibroblasts, SCs, and other cytokines. Further research is needed to understand the nature of the cellular environment, its mechanobiology, and its relationship to the neural insult causing CP, particularly the identification of a mechanism that causes the cellular myopathies as a result of the neural lesion.

CP is complex and cyclical—it is caused by a neural lesion which causes downstream musculoskeletal effects that interact with one another and also interact with the natural processes of growth and aging. While impaired muscular development has been observed at around 15 months of age, atypical movements are noticeable as early as 3 months of age [170], potentially implying that muscle morphology is a downstream effect of altered neural activation and biomechanics, rather than a direct consequence of the neural lesion. Separating these issues in a reductive approach is difficult, but advancements in computational modelling and bioengineering approaches [171, 172] create new advanced possibilities for simulating and understanding these mechanisms.

The very nature of CP makes it subject-specific in its manifestation. Understanding the muscular effects of CP requires approaching the philosophy of CP as an 'umbrella' diagnosis or a grouping of pathologies related only in their initial cause and general scope of resultant symptoms. There should be no expectation of uniformity in the expression of muscular pathology. Nevertheless, continued probing of the mechanisms and interactions of the various muscle pathologies associated with CP will enable us to develop new treatments and therapies that are scientifically based and tailored to the individual and their specific pathology.

Abbreviations

CP: cerebral palsy; MRI: Magnetic Resonance Imaging; SCPE: Surveillance of Cerebral Palsy in Europe; GMFCS: Gross Motor Function Classification System; MACS: Manual Ability Classification System; CFCS: Communication Function Classification System; EDACS: Eating and Drinking Ability Classification System; TD: typically developing; ROM: range of motion; MTU: muscle-tendon unit; PCSA: physiological cross-sectional area; ECM: extracellular matrix; IL-6: interleukin-6; TNF-α: tumor necrosis factor alpha; TGF-ß: transforming growth factor beta; SC: satellite cell; BoNT-A: botulinum neurotoxin-A; SDR: selective dorsal rhizotomy.

Acknowledgments

The authors wish to acknowledge the contributions of the participants with cerebral palsy and their families, whose time and cooperation in prior research studies has led to the advancements in treatment and knowledge that we discuss here.

Authors' contributions

All authors worked collaboratively on the content and organization of this manuscript. GH organized the team of authors, wrote portions of Main Text and abstract, and created figures. SW wrote portions of Main Text and abstract and created figures. SK wrote portions of Main Text and abstract and created figures. GL wrote portions of Main Text and abstract and provided images for figures. NSS wrote portions of Main Text and abstract. All authors reviewed and edited manuscript and contributed to Conclusions section. All authors read and approved the final manuscript.

Funding

The authors are grateful for the funding support provided by the Aotearoa Fellowship from the Robertson Foundation (GH and SK); Cerebral Palsy International, grant no. R-810-13, and Cerebral Palsy Alliance, grant no. CDG213 (GL); and the Australasian Cerebral Palsy Clinical Trials Network—AusCP-CTN—a Centre for Research Excellence funded by the National Health Medical Research Council of Australia (SW and NSS). Funding bodies provided salary, stipend, and lab support for authors; funding bodies were not involved in study design or collection, analysis, interpretation of data, or writing of this article.

Availability of data and materials

All data analyzed in this article are publicly available in the published literature and are cited within our article and bibliography.

Declarations

Ethics approval and consent to participate

Ethics approval was not necessary for the current review article as no new data were collected and all data analyzed were publicly available in the published literature.

Consent for publication

Publication consent is not applicable for this review article as no individual person's data were used here.

Competing interests

The authors have no competing interests or financial conflicts of interest to disclose.

Author details

[1]Auckland Bioengineering Institute, University of Auckland, Auckland CBD, Auckland 1010, New Zealand. [2]Liggins Institute, University of Auckland, Auckland CBD, Auckland 1010, New Zealand. [3]School of Allied Health, Curtin University, Kent St, Bentley, WA 6102, Australia. [4]School of Human Movement and Nutrition Sciences, University of Queensland, QLD, St Lucia 4072, Australia. [5]Department of Surgery, Faculty of Medical and Health Sciences, University of Auckland, Auckland CBD, Auckland 1010, New Zealand.

Received: 6 September 2021 Accepted: 12 February 2022
Published online: 10 March 2022

References

1. Surveillance of cerebral palsy in Europe. Surveillance of cerebral palsy in Europe: a collaboration of cerebral palsy surveys and registers. Surveillance of cerebral palsy in Europe (SCPE). Dev Med Child Neurol. 2000;42.
2. Smithers-Sheedy H, Mcintyre S, Gibson C, Meehan E, Scott H, Goldsmith S, et al. A special supplement: findings from the Australian cerebral palsy register, birth years 1993 to 2006. Dev Med Child Neurol. 2016;58:5–10. https://doi.org/10.1111/dmcn.13026.
3. Van Naarden BK, Doernberg N, Schieve L, Christensen D, Goodman A, Yeargin-Allsopp M. Birth prevalence of cerebral palsy: a population-based study. Pediatrics. 2016;137:e20152872. https://doi.org/10.1542/peds.2015-2872.
4. Andersen GL, Irgens LM, Haagaas I, Skranes JS, Meberg AE, Vik T. Cerebral palsy in Norway: prevalence, subtypes and severity. Eur J Paediatr Neurol. 2008;12:4–13.
5. Stanley FJ, Blair E, Alberman E. Cerebral palsies: epidemiology and causal pathways: Cambridge University Press; 2000.
6. Blair E, Langdon K, McIntyre S, Lawrence D, Watson L. Survival and mortality in cerebral palsy: observations to the sixth decade from a data linkage study of a total population register and National Death Index. BMC Neurol. 2019;19:1–11.
7. Little WJ. Course of lectures on the deformities of the human frame. Lancet. 1844;41:809–15.
8. Little WJ. On the influence of abnormal parturition, difficult labours, premature birth, and asphyxia neonatorum, on the mental and physical condition of the child, especially in relation to deformities. Trans Obstet Soc London. 1861;3:293–344.
9. Morris C. Definition and classification of cerebral palsy: a historical perspective. Dev Med Child Neurol. 2007;49(SUPPL):2.
10. Bax M. Terminology and classification of cerebral palsy. Dev Med Child Neurol. 1964;6:295–7.
11. Mutch L, Alberman E, Hagberg B, Kodama K, Perat MV. Cerebral palsy epidemiology: where are we now and where are we going? Dev Med Child Neurol. 1992;34:547–51.
12. Rosenbaum P, Paneth N, Leviton A, Goldstein M, Bax M. A report: the definition and classification of cerebral palsy April 2006. Dev Med Child Neurol. 2007;49(SUPPL. 2):8–14. https://doi.org/10.1111/j.1469-8749.2007.tb12610.x.
13. Korzeniewski SJ, Birbeck G, DeLano MC, Potchen MJ, Paneth N. A systematic review of neuroimaging for cerebral palsy. J Child Neurol. 2008;23:216–27. https://doi.org/10.1177/0883073807307983.
14. Horber V, Sellier E, Horridge K, Rackauskaite G, Andersen GL, Virella D, et al. The origin of the cerebral palsies: contribution of population-based neuroimaging data. Neuropediatrics. 2020;51:113–9. https://doi.org/10.1055/s-0039-3402007.
15. Himmelmann K, Horber V, De La Cruz J, Horridge K, Mejaski-Bosnjak V, Hollody K, et al. MRI classification system (MRICS) for children with cerebral palsy: development, reliability, and recommendations. Dev Med Child Neurol. 2017;59.
16. Morgan C, Romeo DM, Chorna O, Novak I, Galea C, Del Secco S, et al. The pooled diagnostic accuracy of neuroimaging, general movements, and neurological examination for diagnosing cerebral palsy early in high-risk infants: a case control study. J Clin Med. 2019;8:1879.
17. Pandyan AD, Gregoric M, Barnes MP, Wood D, Van WF, Burridge J, et al. Spasticity : Clinical perceptions , neurological realities and meaningful measurement. Disabil Rehabil. 2005;27:2–6.
18. Malhotra S, Pandyan AD, Day CR, Jones PW, Hermens H. Spasticity, an impairment that is poorly defined and poorly measured. Clin Rehabil. 2009;23:651–8.
19. Bar-On L, Molenaers G, Aertbeliën E, Monari D, Feys H, Desloovere K. The relation between spasticity and muscle behavior during the swing phase of gait in children with cerebral palsy. Res Dev Disabil. 2014;35:3354–64. https://doi.org/10.1016/J.RIDD.2014.07.053.
20. Lance JW. Symposium synopsis. Spasticity Disord mot. Control. 1980:487–9.
21. Shevell MI. The terms diplegia and quadriplegia should not be abandoned. Dev Med Child Neurol. 2010;52.
22. Colver AF, Sethumadhavan T. The term diplegia should be abandoned. Arch Dis Child. 2003;88:286–90.
23. Hurvitz EA, Brown SH. The terms diplegia, quadriplegia, and hemiplegia should be phased out. Dev Med Child Neurol. 2010;52.
24. Sellier E, Horber V, Krägeloh-Mann I, De La Cruz J, Cans C. Interrater reliability study of cerebral palsy diagnosis, neurological subtype, and gross motor function. Dev Med Child Neurol. 2012;54.
25. Cans C, Dolk H, Platt MJ, Colver A, Prasauskiene A, Krägel-Oh-Mann I. Recommendations from the SCPE collaborative group for defining and classifying cerebral palsy. Dev Med Child Neurol. 2007;49(SUPPL):2.
26. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. Dev Med Child Neurol. 1997;39:214–23. https://doi.org/10.1111/j.1469-8749.1997.tb07414.x.
27. Reid SM, Carlin JB, Reddihough DS. Using the gross motor function classification system to describe patterns of motor severity in cerebral palsy. Dev Med Child Neurol. 2011;53:1007–12.
28. Paulson A, Vargus-Adams J. Overview of four functional classification systems commonly used in cerebral palsy. Children. 2017;4.
29. Hadders-Algra M. Neural substrate and clinical significance of general movements: an update. Dev Med Child Neurol. 2018;60:39–46.
30. Olsen JE, Allinson LG, Doyle LW, Brown NC, Lee KJ, Eeles AL, et al. Preterm and term-equivalent age general movements and 1-year neurodevelopmental outcomes for infants born before 30 weeks' gestation. Dev Med Child Neurol. 2018;60:47–53.
31. Herskind A, Ritterband-Rosenbaum A, Willerslev-Olsen M, Lorentzen J, Hanson L, Lichtwark G, et al. Muscle growth is reduced in 15-month-old children with cerebral palsy. Dev Med Child Neurol. 2016;58:485–91. https://doi.org/10.1111/dmcn.12950.
32. Nikolaou S, Peterson E, Kim A, Wylie C, Cornwall R. Impaired growth of denervated muscle contributes to contracture formation following neonatal brachial plexus injury. J Bone Jt Surg - Ser A. 2011;93:461–70.
33. Nooijen C, Slaman J, Van Der Slot W, Stam HJ, Roebroeck ME, Van Den Berg-Emons R. Health-related physical fitness of ambulator yadole scents and young adults with spastic cerebral palsy. J Rehabil Med. 2014;46.
34. McPhee PG, Brunton LK, Timmons BW, Bentley T, Gorter JW. Fatigue and its relationship with physical activity, age, and body composition in adults with cerebral palsy. Dev Med Child Neurol. 2017;59.
35. García CC, Alcocer-Gamboa A, Ruiz MP, Caballero IM, Faigenbaum AD, Esteve-Lanao J, et al. Metabolic, cardiorespiratory, and neuromuscular fitness performance in children with cerebral palsy: a comparison with healthy youth. J Exerc Rehabil. 2016;12.
36. Jacobson DNO, Löwing K, Tedroff K. Health-related quality of life, pain, and fatigue in young adults with cerebral palsy. Dev Med Child Neurol. 2020;62.
37. Verschuren O, Smorenburg ARP, Luiking Y, Bell K, Barber L, Peterson MD. Determinants of muscle preservation in individuals with cerebral palsy across the lifespan: a narrative review of the literature. J Cachexia Sarcopenia Muscle. 2018;9:453–64. https://doi.org/10.1002/jcsm.12287.
38. Graham HK, Rosenbaum P, Paneth N, Dan B, Lin JP, DiL D, et al. Cerebral palsy. Nat Rev Dis Primers. 2016;2.
39. Lee SSM, Gaebler-Spira D, Zhang LQ, Rymer WZ, Steele KM. Use of shear wave ultrasound elastography to quantify muscle properties in cerebral palsy. Clin Biomech. 2016;31:20–8.
40. Graham HK, Selber P. Musculoskeletal aspects of cerebral palsy. J Bone Jt Surg - Ser B. 2003;85:157–66. https://doi.org/10.1302/0301-620X.85B2.14066.
41. Barrett RS, Lichtwark GA. Gross muscle morphology and structure in spastic cerebral palsy: a systematic review. Dev Med Child Neurol. 2010;52:794–804.
42. Lieber RL, Fridén J. Spasticity causes a fundamental rearrangement of muscle-joint interaction. Muscle Nerve. 2002;25:265–70. https://doi.org/10.1002/mus.10036.
43. Lampe R, Grassl S, Mitternacht J, Gerdesmeyer L, Gradinger R. MRT-measurements of muscle volumes of the lower extremities of youths with spastic hemiplegia caused by cerebral palsy. Brain and Development. 2006;28:500–6. https://doi.org/10.1016/j.braindev.2006.02.009.
44. Malaiya R, McNee AE, Fry NR, Eve LC, Gough M, Shortland AP. The morphology of the medial gastrocnemius in typically developing children and children with spastic hemiplegic cerebral palsy. J Electromyogr Kinesiol. 2007;17:657–63. https://doi.org/10.1016/j.jelekin.2007.02.009.

45. Oberhofer K, Stott NS, Mithraratne K, Anderson IA. Subject-specific modelling of lower limb muscles in children with cerebral palsy. Clin Biomech. 2010;25:88–94.
46. Barber L, Hastings-Ison T, Baker R, Barrett R, Lichtwark GA. Medial gastrocnemius muscle volume and fascicle length in children aged 2 to 5 years with cerebral palsy. Dev Med Child Neurol. 2011;53:543–8. https://doi.org/10.1111/j.1469-8749.2011.03913.x.
47. Noble JJ, Fry NR, Lewis AP, Keevil SF, Gough M, Shortland AP. Lower limb muscle volumes in bilateral spastic cerebral palsy. Brain and Development. 2014;36:294–300.
48. Reid SLSL, Pitcher CA, Williams SASA, Licari MK, Valentine JP, Shipman PJ, et al. Does muscle size matter? The relationship between muscle size and strength in children with cerebral palsy. Disabil Rehabil. 2014;37:579–84. https://doi.org/10.3109/09638288.2014.935492.
49. Handsfield GG, Meyer CH, Abel MF, Blemker SS. Heterogeneity of muscle sizes in the lower limbs of children with cerebral palsy. Muscle Nerve. 2016;53:933–45.
50. Sahrmann AS, Stott NS, Besier TF, Fernandez JW, Handsfield GG. Soleus muscle weakness in cerebral palsy: muscle architecture revealed with diffusion tensor imaging. PLoS One. 2019;14:1–16.
51. D'Souza A, Bolsterlee B, Lancaster A, Herbert RD. Muscle architecture in children with cerebral palsy and ankle contractures: an investigation using diffusion tensor imaging. Clin Biomech. 2019;68:205–11.
52. Mathewson MA, Ward SR, Chambers HG, Lieber RL. High resolution muscle measurements provide insights into equinus contractures in patients with cerebral palsy. J Orthop Res. 2015;33:33–9. https://doi.org/10.1002/jor.22728.
53. Smith LR, Lee KS, Ward SR, Chambers HG, Lieber RL. Hamstring contractures in children with spastic cerebral palsy result from a stiffer extracellular matrix and increased in vivo sarcomere length. J Physiol. 2011;589:2625–39.
54. Massaad A, Assi A, Bakouny Z, Bizdikian AJ, Skalli W, Ghanem I. Alterations of treatment-naïve pelvis and thigh muscle morphology in children with cerebral palsy. J Biomech. 2019;82:178–85. https://doi.org/10.1016/j.jbiomech.2018.10.022.
55. Pitcher CA, Elliott CM, Panizzolo FA, Valentine JP, Stannage K, Reid SL. Ultrasound characterization of medial gastrocnemius tissue composition in children with spastic cerebral palsy. Muscle Nerve. 2015;52:397–403. https://doi.org/10.1002/mus.24549.
56. Sartori M, Fernandez JWW, Modenese L, Carty CPP, Barber LAA, Oberhofer K, et al. Toward modeling locomotion using electromyography-informed 3D models: application to cerebral palsy. Wiley Interdiscip Rev Syst Biol Med. 2017;9.
57. Shortland AP, Harris C a, Gough M, Robinson RO. Architecture of the medial gastrocnemius in children with spastic diplegia. Dev Med Child Neurol 2002;44:158.
58. Moreau NG, Holthaus K, Marlow N. Differential adaptations of muscle architecture to high-velocity versus traditional strength training in cerebral palsy. Neurorehabil Neural Repair. 2013;27:325–34. https://doi.org/10.1177/1545968312469834.
59. Barber L, Barrett R, Lichtwark G. Validity and reliability of a simple ultrasound approach to measure medial gastrocnemius muscle length. J Anat. 2011;218:637–42.
60. Mohagheghi AA, Khan T, Meadows TH, Giannikas K, Baltzopoulos V, Maganaris CN. In vivo gastrocnemius muscle fascicle length in children with and without diplegic cerebral palsy. Dev Med Child Neurol. 2008;50:44–50. https://doi.org/10.1111/j.1469-8749.2007.02008.x.
61. Shortland AP, Fry NR, Eve LC, Gough M. Changes to medial gastrocnemius architecture after surgical intervention in spastic diplegia. Dev Med Child Neurol. 2004;46:667–73. https://doi.org/10.1111/j.1469-8749.2004.tb00979.x.
62. Moreau NG, Teefey SA, Damiano DL. In vivo muscle architecture and size of the rectus femoris and vastus lateralis in children and adolescents with cerebral palsy. Dev Med Child Neurol. 2009;51:800–6.
63. Matthiasdottir S, Hahn M, Yaraskavitch M, Herzog W. Muscle and fascicle excursion in children with cerebral palsy. Clin Biomech. 2014;29:458–62.
64. Lichtwark GA, Farris DJ, Chen X, Hodges PW, Delp SL. Microendoscopy reveals positive correlation in multiscale length changes and variable sarcomere lengths across different regions of human muscle. J Appl Physiol. 2018;125:1812–20.
65. Cutts A. The range of sarcomere lengths in the muscles of the human lower limb; 1988.
66. Lieber RL, Loren GJ, Friden J. In vivo measurement of human wrist extensor muscle sarcomere length changes; 1994.
67. Larkin-Kaiser KA, Howard JJ, Leonard T, Joumaa V, Gauthier L, Logan K, et al. Relationship of muscle morphology to hip displacement in cerebral palsy: a pilot study investigating changes intrinsic to the sarcomere. J Orthop Surg Res. 2019;14:187. https://doi.org/10.1186/s13018-019-1239-1.
68. Smeulders MJC, Kreulen M, Hage JJ, Huijing PA, van der Horst CMAM. Overstretching of sarcomeres may not cause cerebral palsy muscle contracture. J Orthop Res. 2004;22:1331–5. https://doi.org/10.1016/j.orthres.2004.04.006.
69. Ateş F, Temelli Y, Yucesoy CA. The mechanics of activated semitendinosus are not representative of the pathological knee joint condition of children with cerebral palsy. J Electromyogr Kinesiol. 2016;28:130–6.
70. Yucesoy CA, Temelli Y, Ateş F. Intra-operatively measured spastic semimembranosus forces of children with cerebral palsy. J Electromyogr Kinesiol. 2017;36:49–55. https://doi.org/10.1016/j.jelekin.2017.07.003.
71. Barber L, Barrett R, Lichtwark G. Medial gastrocnemius muscle fascicle active torque-length and Achilles tendon properties in young adults with spastic cerebral palsy. J Biomech. 2012;45:2526–30. https://doi.org/10.1016/j.jbiomech.2012.07.018.
72. Llewellyn ME, Barretto RPJ, Delp SL, Schnitzer MJ. Minimally invasive high-speed imaging of sarcomere contractile dynamics in mice and humans. Nature. 2008;454:784–8.
73. Chen X, Delp SL. Human soleus sarcomere lengths measured using in vivo microendoscopy at two ankle flexion angles. J Biomech. 2016;49:4164–7. https://doi.org/10.1016/j.jbiomech.2016.11.010.
74. Gao F, Zhao H, Gaebler-Spira D, Zhang L-QQ. In vivo evaluations of morphologic changes of gastrocnemius muscle fascicles and achilles tendon in children with cerebral palsy. Am J Phys Med Rehabil. 2011;90:364–71. https://doi.org/10.1097/PHM.0b013e318214f699.
75. Wren TALL, Cheatwood AP, Rethlefsen SA, Hara R, Perez FJ, Kay RM. Achilles tendon length and medial gastrocnemius architecture in children with cerebral palsy and equinus gait. J Pediatr Orthop. 2010;30:479–84. https://doi.org/10.1097/BPO.0b013e3181e00c80.
76. Barber L, Barrett R, Lichtwark G. Passive muscle mechanical properties of the medial gastrocnemius in young adults with spastic cerebral palsy. J Biomech. 2011;44:2496–500. https://doi.org/10.1016/j.jbiomech.2011.06.008.
77. Theis N, Korff T, Kairon H, Mohagheghi AA. Does acute passive stretching increase muscle length in children with cerebral palsy? Clin Biomech. 2013;28:1061–7. https://doi.org/10.1016/j.clinbiomech.2013.10.001.
78. Kalkman BM, Bar-On L, Cenni F, Maganaris CN, Bass A, Holmes G, et al. Muscle and tendon lengthening behaviour of the medial gastrocnemius during ankle joint rotation in children with cerebral palsy. Exp Physiol. 2018;103:1367–76.
79. Barber LA, Barrett RS, Gillett JG, Cresswell AG, Lichtwark GA. Neuromechanical properties of the triceps surae in young and older adults. Exp Gerontol. 2013;48:1147–55.
80. Chen Y, He L, Xu K, Li J, Guan B, Tang H. Comparison of calf muscle architecture between Asian children with spastic cerebral palsy and typically developing peers. PLoS One. 2018;13:e0190642. https://doi.org/10.1371/journal.pone.0190642.
81. Kruse A, Schranz C, Tilp M, Svehlik M. Muscle and tendon morphology alterations in children and adolescents with mild forms of spastic cerebral palsy. BMC Pediatr. 2018;18:273. https://doi.org/10.1186/s12887-018-1251-3.
82. Barber L, Hastings-Ison T, Baker R, Barrett R, Lichtwark G. Medial gastrocnemius muscle volume and fascicle length in children aged 2 to 5years with cerebral palsy. Dev Med Child Neurol. 2011;53:543–8.
83. Narici MV, Maganaris CN, Reeves ND, Capodaglio P. Effect of aging on human muscle architecture. J Appl Physiol. 2003;95:2229–34.
84. Turton P, Hay R, Taylor J, McPhee J, Welters I. Human limb skeletal muscle wasting and architectural remodeling during five to ten days intubation and ventilation in critical care - an observational study using ultrasound. BMC Anesthesiol. 2016;16:1–8.

85. Kubo K, Kanehisa H, Azuma K, Ishizu M, Kuno SY, Okada M, et al. Muscle architectural characteristics in young and elderly men and women. Int J Sports Med. 2003;24:125–30. https://doi.org/10.1055/s-2003-38204.
86. Lieber RL, Fridén J. Clinical significance of skeletal muscle architecture. Clin Orthop Relat Res. 2001;23:140–51.
87. Schless SH, Cenni F, Bar-On L, Hanssen B, Goudriaan M, Papageorgiou E, et al. Combining muscle morphology and neuromotor symptoms to explain abnormal gait at the ankle joint level in cerebral palsy. Gait Posture. 2019;68:531–7. https://doi.org/10.1016/j.gaitpost.2018.12.002.
88. Schless SH, Cenni F, Bar-On L, Hanssen B, Kalkman B, O'brien T, et al. Medial gastrocnemius volume and echo-intensity after botulinum neurotoxin a interventions in children with spastic cerebral palsy. Dev Med Child Neurol. 2019;61:783–90. https://doi.org/10.1111/dmcn.14056.
89. Cenni F, Bar-On L, Schless SH, Kalkman B, Aertbelien E, Bruyninckx H, et al. Medial Gastrocnemius Muscle–Tendon Junction and Fascicle Lengthening across the Range of Motion Analyzed in 2-D and 3-D Ultrasound Images. Ultrasound Med Biol. 2018;44:2505–18.
90. Obst SJ, Boyd R, Read F, Barber L. Quantitative 3-D ultrasound of the medial gastrocnemius muscle in children with unilateral spastic cerebral palsy. Ultrasound Med Biol. 2017;43:2814–23.
91. Smith LR, Chambers HG, Lieber RL. Reduced satellite cell population may lead to contractures in children with cerebral palsy. Dev Med Child Neurol. 2013;55:264–70.
92. Dayanidhi S, Lieber RL. Muscle biology of contractures in children with cerebral palsy. In: Cerebral palsy: a multidisciplinary approach. 3rd ed: Springer International Publishing; 2018. p. 143–53.
93. De Bruin M, Smeulders MJ, Kreulen M, Huijing PA, Jaspers RT. Intramuscular connective tissue differences in spastic and control muscle: a mechanical and histological study. PLoS One. 2014;9.
94. Marbini A, Ferrari A, Cioni G, Bellanova MF, Fusco C, Gemignani F. Immunohistochemical study of muscle biopsy in children with cerebral palsy. Brain and Development. 2002;24:63–6. https://doi.org/10.1016/S0387-7604(01)00394-1.
95. Von Walden F, Gantelius S, Liu C, Borgström H, Björk L, Gremark O, et al. Muscle contractures in patients with cerebral palsy and acquired brain injury are associated with extracellular matrix expansion, pro-inflammatory gene expression, and reduced rRNA synthesis. Muscle Nerve. 2018;58:277–85.
96. Rose J, Haskell WL, Gamble JG, Hamilton RL, Brown D, a, Rinsky L. Muscle pathology and clinical measures of disability in children with cerebral palsy. J Orthop Res. 1994;12:758–68.
97. Domenighetti AA, Mathewson MA, Pichika R, Sibley LA, Zhao L, Chambers HG, et al. Loss of myogenic potential and fusion capacity of muscle stem cells isolated from contractured muscle in children with cerebral palsy. Am J Physiol Cell Physiol. 2018;315:C247–57.
98. Kinney MC, Dayanidhi S, Dykstra PB, McCarthy JJ, Peterson CA, Lieber RL. Reduced skeletal muscle satellite cell number alters muscle morphology after chronic stretch but allows limited serial sarcomere addition. Muscle Nerve. 2017;55:384–92.
99. Murphy MM, Lawson JA, Mathew SJ, Hutcheson DA, Kardon G. Satellite cells, connective tissue fibroblasts and their interactions are crucial for muscle regeneration. Development. 2011;138:3625–37.
100. Smith LR, Pontén E, Hedström Y, Ward SR, Chambers HG, Subramaniam S, et al. Novel transcriptional profile in wrist muscles from cerebral palsy patients. BMC Med Genet. 2009;2:44.
101. Bonnieu A, Carnac G, Vernus B. Myostatin in the pathophysiology of skeletal muscle. Curr Genomics. 2009;8:415–22. https://doi.org/10.2174/138920207783591672.
102. Burks TN, Cohn RD. Role of TGF-β signaling in inherited and acquired myopathies. Skelet Muscle. 2011;1:19. https://doi.org/10.1186/2044-5040-1-19.
103. Kirk S, Oldham J, Kambadur R, Sharma M, Dobbie P, Bass J. Myostatin regulation during skeletal muscle regeneration. J Cell Physiol. 2000;184:356–63.
104. Snijders T, Nederveen JP, McKay BR, Joanisse S, Verdijk LB, van Loon LJC, et al. Satellite cells in human skeletal muscle plasticity. Front Physiol. 2015;6:OCT. https://doi.org/10.3389/fphys.2015.00283.
105. Zhao BL, Kollias HD, Wagner KR. Myostatin directly regulates skeletal muscle fibrosis. J Biol Chem. 2008;283:19371–8.
106. Mackey AL, Magnan M, Chazaud B, Kjaer M. Human skeletal muscle fibroblasts stimulate in vitro myogenesis and in vivo muscle regeneration. J Physiol. 2017;595:5115–27.
107. Frantz C, Stewart KM, Weaver VM. The extracellular matrix at a glance. J Cell Sci. 2010;123:4195–200. https://doi.org/10.1242/jcs.023820.
108. Gillies AR, Lieber RL. Structure and function of the skeletal muscle extracellular matrix. Muscle Nerve. 2011;44:318–31.
109. Mendias CL. Fibroblasts take the Centre stage in human skeletal muscle regeneration. J Physiol. 2017;595:5005. https://doi.org/10.1113/JP274403.
110. Booth CM, Cortina-Borja MJF, Theologis TN. Collagen accumulation in muscles of children with cerebral palsy and correlation with severity of spasticity. Dev Med Child Neurol. 2001;43:314–20. https://doi.org/10.1111/j.1469-8749.2001.tb00211.x.
111. Webster MT, Manor U, Lippincott-Schwartz J, Fan CM. Intravital imaging reveals ghost fibers as architectural units guiding myogenic progenitors during regeneration. Cell Stem Cell. 2016;18:243–52. https://doi.org/10.1016/j.stem.2015.11.005.
112. Contreras O, Rebolledo DL, Oyarzún JE, Olguín HC, Brandan E. Connective tissue cells expressing fibro/adipogenic progenitor markers increase under chronic damage: relevance in fibroblast-myofibroblast differentiation and skeletal muscle fibrosis. Cell Tissue Res. 2016;364:647–60. https://doi.org/10.1007/s00441-015-2343-0.
113. Noble JJ, Charles-Edwards GD, Keevil SF, Lewis AP, Gough M, Shortland AP. Intramuscular fat in ambulant young adults with bilateral spastic cerebral palsy. BMC Musculoskelet Disord. 2014;15:1–8.
114. Shortland A. Muscle deficits in cerebral palsy and early loss of mobility: can we learn something from our elders? Dev Med Child Neurol. 2009;51(SUPPL. 4):59–63. https://doi.org/10.1111/j.1469-8749.2009.03434.x.
115. Willerslev-Olsen M, Choe Lund M, Lorentzen J, Barber L, Kofoed-Hansen M, Nielsen JB. Impaired muscle growth precedes development of increased stiffness of the triceps surae musculotendinous unit in children with cerebral palsy. Dev Med Child Neurol. 2018;60:672–9. https://doi.org/10.1111/dmcn.13729.
116. Zwier JN, Van Schie PEM, Becher JG, Smits D-W, Gorter JW, Dallmeijer AJ. Physical activity in young children with cerebral palsy. Disabil Rehabil. 2010;32:1501–8.
117. den Berg-Emons HJG, Saris WHM, De Barbanson DC, Westerterp KR, Huson A, Van Baak MA. Daily physical activity of schoolchildren with spastic diplegia and of healthy control subjects. J Pediatr. 1995;127:578–84.
118. Stevens SL, Holbrook EA, Fuller DK, Morgan DW. Influence of age on step activity patterns in children with cerebral palsy and typically developing children. Arch Phys Med Rehabil. 2010;91:1891–6.
119. Bjornson KF, Belza B, Kartin D, Logsdon R, McLaughlin JF. Ambulatory physical activity performance in youth with cerebral palsy and youth who are developing typically. Phys Ther. 2007;87:248–57.
120. Maher CA, Williams MT, Olds T, Lane AE. Physical and sedentary activity in adolescents with cerebral palsy. Dev Med Child Neurol. 2007;49:450–7.
121. Bell KL, Davies PSW. Energy expenditure and physical activity of ambulatory children with cerebral palsy and of typically developing children. Am J Clin Nutr. 2010;92:313–9.
122. Bjornson KF, Zhou C, Stevenson R, Christakis D, Song K. Walking activity patterns in youth with cerebral palsy and youth developing typically. Disabil Rehabil. 2014;36:1279–84. https://doi.org/10.3109/09638288.2013.845254.
123. Theis N, Brown MA, Wood P, Waldron M. Leucine supplementation increases muscle strength and volume, reduces inflammation, and affects wellbeing in adults and adolescents with cerebral palsy. J Nutr. 2020. https://doi.org/10.1093/jn/nxaa006.
124. Day SM, Strauss DJ, Vachon PJ, Rosenbloom L, Shavelle RM, Wu YW. Growth patterns in a population of children and adolescents with cerebral palsy. Dev Med Child Neurol. 2007;49:167–71.
125. Brooks J, Day S, Shavelle R, Strauss D. Low weight, morbidity, and mortality in children with cerebral palsy: new clinical growth charts. Pediatrics. 2011;128:e299–307.
126. Murphy KP. The adult with cerebral palsy. Orthop Clin North Am. 2010;41:595–605.

127. Day SM, Wu YW, Strauss DJ, Shavelle RM, Reynolds RJ. Change in ambulatory ability of adolescents and young adults with cerebral palsy. Dev Med Child Neurol. 2007;49:647–53.
128. Andersson C, Mattsson E. Adults with cerebral palsy: a survey describing problems, needs, and resources, with special emphasis on locomotion. Dev Med Child Neurol. 2001;43:76–82. https://doi.org/10.1017/S0012162201.
129. Jahnsen R, Villien L, Egeland T, Stanghelle JK, Holm I. Locomotion skills in adults with cerebral palsy. Clin Rehabil. 2004;18:309–16. https://doi.org/10.1191/0269215504cr735oa.
130. Bottos M, Feliciangeli A, Sciuto L, Gericke C, Vianello A. Functional status of adults with cerebral palsy and implications for treatment of children. Dev Med Child Neurol. 2007;43:516–28. https://doi.org/10.1111/j.1469-8749.2001.tb00755.x.
131. Opheim A, Jahnsen R, Olsson E, Stanghelle JK. Walking function, pain, and fatigue in adults with cerebral palsy: a 7-year follow-up study. Dev Med Child Neurol. 2009;51:381–8. https://doi.org/10.1111/j.1469-8749.2008.03250.x.
132. Chiu HC, Ada L, Butler J, Coulson S. Relative contribution of motor impairments to limitations in activity and restrictions in participation in adults with hemiplegic cerebral palsy. Clin Rehabil. 2010;24:454–62. https://doi.org/10.1177/0269215509353263.
133. Novak I, Morgan C, Fahey M, Finch-Edmondson M, Galea C, Hines A, et al. State of the evidence traffic lights 2019: systematic review of interventions for preventing and treating children with cerebral palsy. Curr Neurol Neurosci Rep. 2020;20. https://doi.org/10.1007/s11910-020-1022-z.
134. Boyd RN, Hays RM. Current evidence for the use of botulinum toxin type a in the management of children with cerebral palsy: a systematic review. Eur J Neurol. 2001;8:1–20. https://doi.org/10.1046/j.1468-1331.2001.00034.x.
135. Blumetti FC, Belloti JC, Tamaoki MJ, Pinto JA. Botulinum toxin type a in the treatment of lower limb spasticity in children with cerebral palsy. Cochrane Database Syst Rev. 2019. https://doi.org/10.1002/14651858.cd001408.pub2.
136. Multani I, Manji J, Hastings-Ison T, Khot A, Graham K. Botulinum toxin in the Management of Children with cerebral palsy. Pediatr Drugs. 2019;21:261–81. https://doi.org/10.1007/s40272-019-00344-8.
137. Williams SA, Reid S, Elliott C, Shipman P, Valentine J. Muscle volume alterations in spastic muscles immediately following botulinum toxin type-a treatment in children with cerebral palsy. Dev Med Child Neurol. 2013;55:813–20. https://doi.org/10.1111/dmcn.12200.
138. Alexander C, Elliott C, Valentine J, Stannage K, Bear N, Donnelly CJ, et al. Muscle volume alterations after first botulinum neurotoxin a treatment in children with cerebral palsy: a 6-month prospective cohort study. Dev Med Child Neurol. 2018;60:1165–71. https://doi.org/10.1111/dmcn.13988.
139. Williams SA, Elliott C, Valentine J, Gubbay A, Shipman P, Reid S. Combining strength training and botulinum neurotoxin intervention in children with cerebral palsy: the impact on muscle morphology and strength. Disabil Rehabil. 2013;35:596–605. https://doi.org/10.3109/09638288.2012.711898.
140. Fortuna R, Aurélio Vaz M, Rehan Youssef A, Longino D, Herzog W. Changes in contractile properties of muscles receiving repeat injections of botulinum toxin (Botox). J Biomech. 2011;44.
141. Ma J, Elsaidi GA, Smith TL, Walker FO, Tan KH, Martin E, et al. Time course of recovery of juvenile skeletal muscle after botulinum toxin a injection: an animal model study. Am J Phys Med Rehabil. 2004;83.
142. Barber L, Hastings-Ison T, Baker R, Kerr Graham H, Barrett R, Lichtwark G. The effects of botulinum toxin injection frequency on calf muscle growth in young children with spastic cerebral palsy: a 12-month prospective study. J Child Orthop. 2013;7.
143. Van Campenhout A, Verhaegen A, Pans S, Molenaers G. Botulinum toxin type a injections in the psoas muscle of children with cerebral palsy: muscle atrophy after motor end plate-targeted injections. Res Dev Disabil. 2013;34.
144. Gough M, Fairhurst C, Shortland AP. Botulinum toxin and cerebral palsy: time for reflection? Dev Med Child Neurol. 2005;47.
145. Graham HK, Rodda JM. Botulinum toxin and cerebral palsy: time for reflection? Dev Med Child Neurol. 2006;48.
146. Steinbok P. Selective dorsal rhizotomy for spastic cerebral palsy: a review. Childs Nerv Syst. 2007;23:981–90.
147. Lumbosacral Dorsal Rhizotomy for Spastic Cerebral Palsy: A Health Technology Assessment. Ontario health technology assessment series. 2017;17.
148. Wright FV, Sheli EMH, Drake JM, Wedge JH, Naumann S. Evaluation of selective dorsal rhizotomy for the reduction of spasticity in cerebral palsy: a randomised controlled trial. Dev Med Child Neurol. 1998;40.
149. McLaughlin JF, Bjornson KF, Temkin N, Steinbok P, Wright V, Reiner A, et al. Selective dorsal rhizotomy: meta-analysis of three randomized controlled trials. Dev Med Child Neurol. 2002;40:220–32.
150. Nordmark E, Josenby AL, Lagergren J, Andersson G, Strömblad LG, Westbom L. Long-term outcomes five years after selective dorsal rhizotomy. BMC Pediatr. 2008;8.
151. Tedroff K, Löwing K, Åström E. A prospective cohort study investigating gross motor function, pain, and health-related quality of life 17 years after selective dorsal rhizotomy in cerebral palsy. Dev Med Child Neurol. 2015;57.
152. Grunt S, Fieggen AG, Vermeulen RJ, Becher JG, Langerak NG. Selection criteria for selective dorsal rhizotomy in children with spastic cerebral palsy: a systematic review of the literature. Dev Med Child Neurol. 2014;56.
153. Abel MF, Damiano DL, Pannunzio M, Bush J. Muscle-tendon surgery in diplegic cerebral palsy: functional and mechanical changes. J Pediatr Orthop. 1999;19:366–75.
154. Fry NR, Gough M, McNee AE, Shortland AP. Changes in the volume and length of the medial gastrocnemius after surgical recession in children with spastic diplegic cerebral palsy. J Pediatr Orthop. 2007;27:769–74. https://doi.org/10.1097/BPO.0b013e3181558943.
155. Haberfehlner H, Jaspers RT, Rutz E, Harlaar J, Van Der Sluijs JA, Witbreuk MM, et al. Outcome of medial hamstring lengthening in children with spastic paresis: a biomechanical and morphological observational study. PLoS One. 2018;13.
156. Katalinic OM, Harvey LA, Herbert RD, Moseley AM, Lannin NA, Schurr K. Stretch for the treatment and prevention of contractures. Cochrane Database Syst Rev. 2010.
157. Gough M. Serial casting in cerebral palsy: panacea, placebo, or peril? Dev Med Child Neurol. 2007;49:725. https://doi.org/10.1111/j.1469-8749.2007.00725.x.
158. Kalkman BM, Bar-On L, O'Brien TD, Maganaris CN. Stretching interventions in children with cerebral palsy: why are they ineffective in improving muscle function and how can we better their outcome? Front Physiol. 2020;11.
159. Hösl M, Böhm H, Arampatzis A, Döderlein L. Effects of ankle–foot braces on medial gastrocnemius morphometrics and gait in children with cerebral palsy. J Child Orthop. 2015;9:209–19. https://doi.org/10.1007/s11832-015-0664-x.
160. McNee AE, Gough M, Morrissey MC, Shortland AP. Increases in muscle volume after plantarflexor strength training in children with spastic cerebral palsy. Dev Med Child Neurol. 2009;51:429–35. https://doi.org/10.1111/j.1469-8749.2008.03230.x.
161. Stackhouse SK, Binder-Macleod SA, Stackhouse CA, McCarthy JJ, Prosser LA, Lee SCK. Neuromuscular electrical stimulation versus volitional isometric strength training in children with spastic diplegic cerebral palsy: a preliminary study. Neurorehabil Neural Repair. 2007;21:475–85. https://doi.org/10.1177/1545968306298932.
162. Damiano DL, Prosser LA, Curatalo LA, Alter KE. Muscle plasticity and ankle control after repetitive use of a functional electrical stimulation device for foot drop in cerebral palsy. Neurorehabil Neural Repair. 2013;27:200–7. https://doi.org/10.1177/1545968312461716.
163. Pool D, Elliott C, Bear N, Donnelly CJ, Davis C, Stannage K, et al. Neuromuscular electrical stimulation-assisted gait increases muscle strength and volume in children with unilateral spastic cerebral palsy. Dev Med Child Neurol. 2016;58:492–501. https://doi.org/10.1111/dmcn.12955.
164. Gillett JG, Lichtwark GA, Boyd RN, Barber LA. Functional anaerobic and strength training in young adults with cerebral palsy. Med Sci Sports Exerc. 2018;50:1549–57. https://doi.org/10.1249/MSS.0000000000001614.
165. Scholtes VA, Becher JG, Comuth A, Dekkers H, Van Dijk L, Dallmeijer AJ. Effectiveness of functional progressive resistance exercise strength training on muscle strength and mobility in children with

cerebral palsy: a randomized controlled trial. Dev Med Child Neurol. 2010;52:107–13.
166. Moreau NG, Bodkin AW, Bjornson K, Hobbs A, Soileau M, Lahasky K. Effectiveness of rehabilitation interventions to improve gait speed in children with cerebral palsy: systematic review and Meta-analysis. Phys Ther. 2016;96.
167. Verschuren O, Ada L, Maltais DB, Gorter JW, Scianni A, Ketelaar M. Muscle strengthening in children and adolescents with spastic cerebral palsy: considerations for future resistance training protocols. Phys Ther. 2011;91:1130–9.
168. Novak I, Mcintyre S, Morgan C, Campbell L, Dark L, Morton N, et al. A systematic review of interventions for children with cerebral palsy: state of the evidence. Dev Med Child Neurol. 2013;55:885–910.
169. Booth ATC, Buizer AI, Meyns P, Oude Lansink ILB, Steenbrink F, van der Krogt MM. The efficacy of functional gait training in children and young adults with cerebral palsy: a systematic review and meta-analysis. Dev Med Child Neurol. 2018;60.
170. Einspieler C, Marschik PB, Bos AF, Ferrari F, Cioni G, Fr PH. Early markers for cerebral palsy: insights from the assessment of general movements. Futur Neurol. 2012;7:709–17. https://doi.org/10.2217/FNL.12.60.
171. Mills RJ, Parker BL, Monnot P, Needham E., Vivien CJ, Ferguson C, et al. Development of a human skeletal micro muscle platform with pacing capabilities. Biomaterials 2019;198 March 2018:217–227. https://doi.org/10.1016/j.biomaterials.2018.11.030.
172. Khuu S, Fernandez JW, Handsfield GG. A coupled Mechanobiological model of muscle regeneration in cerebral palsy. Front Bioeng. Biotechnol. 2021;9.

Publisher's Note