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INVITED REVIEW

What causes increased passive stiffness of plantarflexor muscle–tendon unit in children with spastic cerebral palsy?

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Abstract

Purpose The term 'stiffness' is commonly used in the literature to refer to various components of 'hyperresistance' by which spastic muscles oppose to their passive lengthening, especially in children with cerebral palsy (CP). Originally, stiffness consists of mechanical resistance to passive movement in the absence of any muscle activation. Increased muscle stiffness in CP therefore refers to alterations to the mechanical properties of the tissue. It is closely linked to muscle shortening, yet the two phenomena are not equivalent. Both increased stiffness and shortening are present early in childhood in the plantarflexor muscles of children with spastic CP.

Methods This narrative review provides a comprehensive overview of the literature on passive stiffness of the plantarflexor muscles measured at the joint, muscles, fascicles, and fiber level in children with CP. Articles were searched through the Pub'Med database using the keywords "cerebral palsy" AND "stiffness".

Result The ambiguous use of the term 'stiffness' has been supported by discrepancies in available results, influenced by heterogeneity in materials, methodologies and characteristics of the participants among studies. Increased stiffness at the joint and muscle belly level may be explained by altered structural properties at the microscopic level.

Conclusion This thorough investigation of the literature suggests that the pathophysiology and the time course of the development of stiffness and contracture remain to be elucidated. A consideration of both morphological and mechanical measurements in children with CP is important when describing the alterations in their plantarflexors.

Keywords Stiffness · Plantarflexors · Cerebral palsy · Children · Contracture

Abbreviations

AT	Achilles tendon
CP	Cerebral palsy
DF	Dorsiflexion
ECM	Extracellular matrix
GL	Gastrocnemius lateralis
GM	Gastrocnemius medialis
GMFCS	Gross motor function classification system
PF	Plantarflexors
SWE	Shear wave elastography
TD	Typically developing

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Introduction

Cerebral palsy (CP) refers to motor impairments after brain damage occurring perinatally (Rosenbaum et al. 2007), with a prevalence of 1.7 per 1000 live births in Europe (Sellier et al. 2016). Spastic CP, where the brain lesions affect the corticospinal pathways, is the most frequent form of CP (Bax et al. 2005; Cahill-Rowley and Rose 2014). From a neuromuscular point of view, spastic CP is the combination of four interrelated alterations: impaired selective motor control, muscle weakness, spasticity, and short muscle–tendon unit length (Cahill-Rowley and Rose 2014). As can be perceived by the clinician, the plantarflexor (PF) muscles are commonly affected in children with spastic CP and are highly subjected to increased resistance to passive elongation

(Bar-On et al. 2015) and decreased range of motion (Hägglund and Wagner 2011). It is then of importance to distinguish the neural (central nervous system related) from the non-neural (tissue related) origins of increased PF resistance to passive lengthening in an attempt to better define therapeutic strategies (Bar-On et al. 2015). This remains, however, very challenging for clinicians and researchers because of the highly complex nature of these impairments and the many potential disorders that can be involved (Bar-On et al. 2015; Gracies 2005). For instance, a confusion still exists in the literature between different neurological or non-neurological disorders such as "spasticity", "stiffness", "abnormal muscle tone", "hypertonia" or "intermittent or sustained involuntary activation of muscles" (Malhotra et al. 2009). This recently led a European consensus of experts to emphasize the neutral term of "hyper-resistance", defined as impaired neuromuscular response to passive muscle stretch in subjects with neurological disorders (van den Noort et al. 2017). The authors further defined "spasticity" as a velocity-dependent stretch hyperreflexia (van den Noort et al. 2017). This distinction should clarify which source of resistance the researchers are investigating in future studies: its neural component (relying on involuntary activation of muscles, creating a resistive torque during externally induced lengthening), or its non-neural component (i.e., the passive mechanical properties of the muscle that is stretched).

Spasticity has been extensively investigated in children with CP. For decades, many studies have contributed to describe its pathophysiology (Bar-On et al. 2015; Gracies 2005), the psychometric properties of its clinical and instrumental assessment (Bar-On et al. 2014a; Scholtes et al. 2005), as well as the effectiveness of treatments targeting it (Bar-On et al. 2014b; Desloovere et al. 2012). In contrast, less attention has been given to the investigation of the mechanical properties of the muscle–tendon unit. Besides altered muscle morphology and structure in children with CP (Barrett and Lichtwark 2010), mechanical properties such as passive stiffness should also be considered. However, the term stiffness has been used to describe various morphological and mechanical properties of the muscle, such as elasticity, viscosity, or even shortening (van den Noort et al. 2017). For example, Farmer and James (2001) defined contracture as 'a decrease in muscle length and an increase in passive muscle stiffness', therefore assuming that increased stiffness is a component of contracture. This entanglement is an obstacle to the access to clear evidence on the issue of stiffness in pathological muscles.

Surprisingly, ankle joint passive stiffness, firstly introduced by Tardieu et al. (1982), has not been investigated in children with CP in a comprehensive manner, so that unequivocal conclusions cannot be made. However, increased ankle joint passive stiffness has been commonly reported in many patients with neurological disorders such as stroke (Gao et al. 2009; Sinkjær and Magnussen 1994), multiple sclerosis (Sinkjér et al. 1993), or in adults with CP (Geertsen et al. 2015). Moreover, increased ankle joint passive stiffness has been reported to alter gait pattern (Geertsen et al. 2015; Marsden et al. 2012), with a high incidence of equinus gait in the population of children with CP (Cobeljic et al. 2009; Goldstein and Harper 2007).

Excessive pressure on the metatarsal heads, increased ankle plantarflexion moments leading to knee hyperextension, and reduced ankle plantarflexion at push-off are the main features of equinus gait (Gage et al. 2009; Perry 1992). The pathophysiology of equinus in children with CP is not fully understood yet (Pingel et al. 2017) and we assume that a long-lasting confusion between what stiffness is, and what it is not, has been a major cause of misunderstanding and impediment to the understanding of equinus in children with CP. It is highly speculated that a combination of impairment of muscle growth and subsequent altered muscle adaptation (e.g., fatty infiltration, fibrosis, increase of collagen content) are involved in this process (Gough and Shortland 2012). However, both phenomena may be responsible for increased muscle passive tension and reduced lengthening capacity. Muscle stiffness of the plantarflexors therefore appears as an issue that is globally considered as highly relevant for all caregivers who deal with motor impairment and limitations in locomotor function in children with CP. A strict definition of the term stiffness and how it could be measured and distinguished from muscle shortening may help clinicians and researchers to understand the mechanisms underlying equinus.

Here, we consider passive stiffness as a measure of stretch resistance without any muscle activation, according to its mechanical definition (see Fig. 1). On the other hand, muscle contracture of the plantarflexors is defined as a reduction in the dorsiflexion range of motion at the ankle, as measured clinically. Considering the whole joint, passive resistance is the result of passive lengthening of several different anatomical structures (i.e., joint capsule, muscles, tendons, skin, fascia, or ligaments), among which muscles are considered to be the primary contributor (Lieber et al. 2017). As defined above, passive stiffness is usually measured by establishing torque–angle curves, which can be coupled with 2D ultrasonography to specifically estimate muscle and tendon stiffness. An alternative method, called shear wave elastography (SWE), is now widely used. It allows measuring a level of tension in a specific tissue such as a superficial muscle or tendon.

In an attempt to perform an integrative overview of the concept of stiffness, including its difference from muscle shortening and its link with the development of such shortening/contracture in children with CP, the present review aims at describing the available data about PF muscle length and stiffness at different levels (i.e., joint, muscle, tendon,

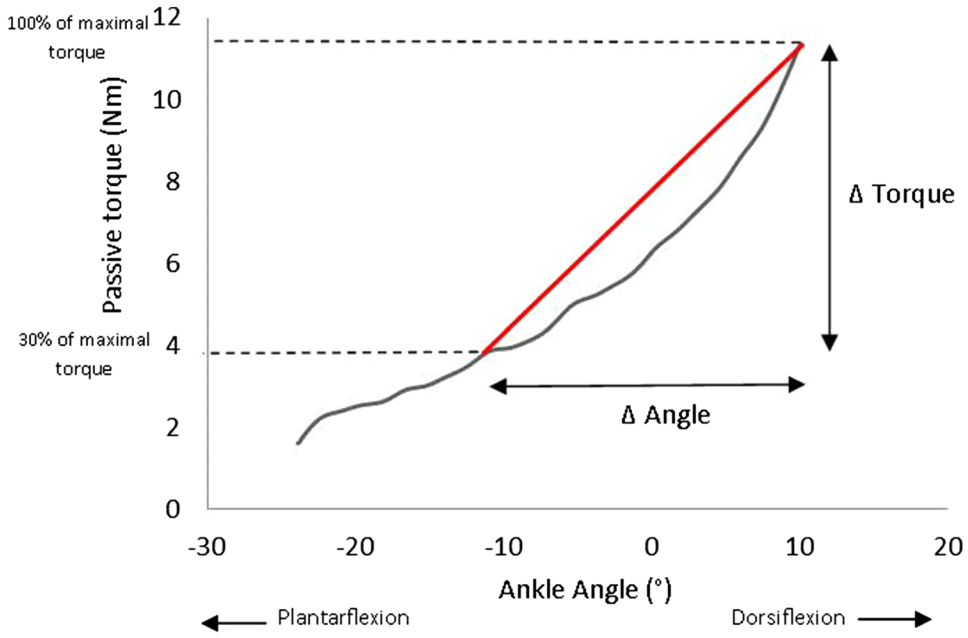

Fig. 1 Example of a torque–angle relationship obtained during passive mobilization of the ankle joint at 2°/s on a paretic leg in a child with unilateral spastic CP. Ankle angle was measured between the tibia and the foot sole. Ankle joint stiffness (ΔTorque/ΔAngle) was measured as the slope of the torque–angle relationship (grey line) between 30 and 100% of the maximal torque recorded (Barber et al. 2011). Personal data from our research team

fascicles, fibers, sarcomeres). We try to present the data in this hierarchical manner, from the overall clinical impairment to the microscopic alterations in muscles, to enhance the potential translational value of the present review. We assume that understanding why muscle stiffness remains such an unraveled phenomenon to date will help point out the gaps in current knowledge and provide insights into the perspectives of future research.

Articles were searched through the PubMed database (up to April 2019) using the keywords "cerebral palsy" AND "stiffness". Articles were then checked for pertinent content and included in the current review when investigating passive stiffness of PF muscles in children with CP. Further articles were considered after scanning the reference lists of the included articles. Only articles that were published in English were included.

Passive ankle joint stiffness

For decades, researchers have investigated joint resistance to passive stretch by recording torque at the joint level during slow mobilization. By establishing torque–angle curves (Fig. 1), one may calculate joint passive stiffness as the slope of the relationship. Passive stiffness (expressed in Nm/° or Nm/rad) then represents the ratio of change in passive resistance (i.e., passive torque) to change in joint angle (Gajdosik 2001). From a mechanical perspective, it is fundamental to consider that establishing such relationships between torque or force, on one hand, and angle or length, on the other, is mandatory to use the word 'stiffness'. Though it relies on instrumental measures (dynamometer), the calculation of torque/angle relationships is a convenient and easy-to-implement method to assess stiffness at the overall joint level. Moreover, it is easily interpreted by the clinicians, as it is related to the phenomena that are evaluated clinically (where resistance and range of motion are rated while performing passive ankle dorsiflexion manoeuvers) and fits the data provided by gait analysis laboratories (where kinematics and kinetics are measured and computed at the joint level).

Tardieu et al. (1982) were the first to report increased stretch resistance of the ankle (i.e., joint passive stiffness) in children with CP. They also demonstrated a more plantarflexed position of the slack angle (the angle where the joint moment, measured by the dynamometer, starts to rise, as a consequence of the onset of tension within the anatomical components) in children with CP. Thereafter, increased ankle joint passive stiffness in children with CP was confirmed by other studies (Alhusaini et al. 2010; Barber et al. 2011; de Gooijer-van de Groep et al. 2013), though one study found similar stiffness in both populations (Kruse et al. 2017) and two studies found mitigated, heterogeneous results (Ross et al. 2011; Willerslev-Olsen et al. 2013). Few studies provided detailed data about the relationship between clinically assessed ankle contracture and ankle stiffness. De Gooijer-van de Groep et al. 2013 found a significant (negative) relationship between the slope of the torque–angle curve and the maximal ankle joint dorsiflexion (DF) angle, with the knee flexed, in 15 year-old-children with CP. In this study, ankle joint stiffness explained 84% of the total variance of ankle range of motion (de Gooijer-van de Groep et al. 2013). More recently, Willerslev-Olsen et al. (2018) found a moderate

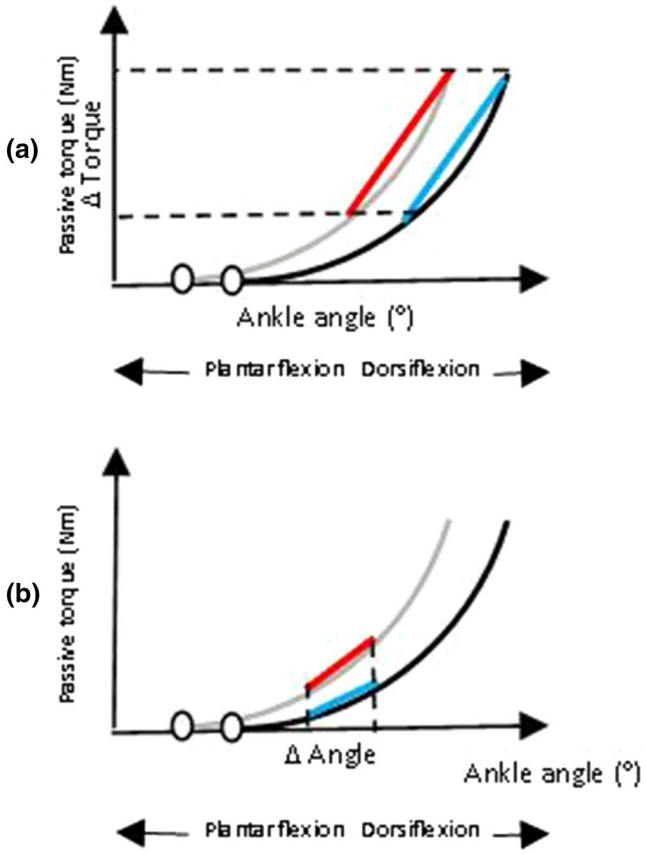

Fig. 2 Examples of torque–angle relationship in children with CP (grey line) with reduced maximal DF angle and a more plantarflexed slack angle (circle) compared to peers with TD (black line). Ankle angle was represented by the angle between the tibia and the foot sole. Ankle joint stiffness value may be similar between children with CP and TD when calculated on the same relative torque range (**a**) or increased in children with CP when calculated on the same absolute range of angle (**b**). Children with CP in this example present with ankle contracture (reduced maximal dorsiflexion angle) and a reduced slack angle. The stiffness of their ankle will be considered as higher than the stiffness in children with TD if method (**b**) is used, while it will be considered as normal if method (**a**) is used. Actually, the shapes of the two torque–angle curves obtained from the two samples are the same, but the curve of the children with CP is "shifted to the left" relative to curve of the children with TD. Therefore, in this example, it should be concluded that children with CP present with ankle contracture, but not with increased ankle stiffness as the passive mechanical properties assessed by the torque–angle relationship do not differ. Torque–angle curves have been obtained based on the outcomes from the literature in children with CP (Alhusaini et al. 2010; Ross et al. 2011)

(negative) correlation between passive stiffness and maximal DF angle in very young children (i.e., under 29 months) with CP. However, Tardieu et al. (1982) in their pioneering work, did not find any correlation between increased passive stiffness and decreased maximal DF angle in children with CP with ankle contracture. The children with CP in this latter study had however severe ankle contracture (mean maximal DF angle: − 9°), which might explain the lack of correlation.

Many parameters have to be taken into account before interpreting torque–angle relationships and may explain the discrepancies between results in the previously mentioned studies. Some are methodological considerations, while the others are intrinsically linked to the subjects who undergo the assessments.

Regarding methodological issues, despite that the measure of passive stiffness was determined using a linear method (i.e., Δtorque/Δangle) in the majority of studies, the method of stiffness calculation differs between them according to the choice of the angle or torque range [e.g., between 30 and 100%, 20% and 80% and 50 and 90% of range of maximal torque for Barber et al. (2011), Theis et al. (2015) and Kruse et al. (2017), respectively; between 5° and 10° vs. on the last 20° of dorsiflexion angle for Alhusaini et al. (2010) vs. Ross et al. (2011)]. Considering this heterogeneity of methods, a part of the "toe region" (the beginning of the curve, corresponding to the initially non-linear increase in passive torque during ankle dorsiflexion) may be included in the analysis in some cases. However, how the "toe region" of the torque–angle curve influences passive stiffness measurement

remains unclear. The fact that stiffness has to be evaluated on a range of ankle angles makes it highly sensible to the choice of this range and to the presence of associated muscle shortening. In other words, passive stiffness outcomes are strongly influenced by the range that is used for slope calculation (Ross et al. 2011). The assessment of ankle joint passive stiffness in both children with CP and TD by considering the slope on the same absolute angle range, despite differences in maximal DF angle and slack angle, may lead to a comparison of different portions of the torque–angle curve. Indeed, passive ankle range of motion and maximal DF angle dramatically decrease during childhood in children with CP (Hägglund and Wagner 2011). This consists in PF muscles contractures, potentially as a consequence of a mismatch between bone and musculo-tendinous unit growth velocity (Švehlík et al. 2013). Consequently, as the PF muscles become short, maximal ankle dorsiflexion is reduced, and the torque–angle relationship curve is shifted toward plantarflexion. Hence, if stiffness is assessed on a common absolute range of motion, the slope of the curve would be systematically higher for children with CP having lower maximal DF angle (Fig. 2) (Ross et al. 2011). Ankle joint passive stiffness has not been investigated in children with CP in a consistent manner, so that unequivocal conclusions cannot be made. This may explain why Alhusaini et al. (2010) found that ankle joint passive stiffness in 7-year-old children with spastic CP was 225% higher than age-matched children with TD, while it was reported to be 51% higher in 17-year-old young adults (i.e., when assessing stiffness on a given relative torque range) (Barber et al. 2011) and 110% higher in 14-year-old teenagers with spastic CP (i.e., when assessing stiffness on a torque range, starting in a neutral 0°–DF angle position) (de Gooijer-van de Groep et al. 2013). Findings reporting an association of increased passive stiffness, decreased slack angle, and reduced maximal dorsiflexion (Barber et al. 2011; Tardieu et al. 1982), suggest that both shortening and altered mechanical properties (increased stiffness) may be present in older children with CP. Their association likely explains the difficulty to obtain unequivocal results about stiffness of the PF in this population (see above). Besides methods used to calculate joint stiffness, the influence of material and angular velocities has to be considered. To establish torque–angle relationships, isokinetic dynamometers were usually used to strictly control angular velocity and joint positioning (Barber et al. 2011; de Gooijer-van de Groep et al. 2013; Ross et al. 2011; Willerslev-Olsen et al. 2013). However, in some studies, a custom-made device was used (Alhusaini et al. 2010; Tardieu et al. 1982). As the experimental procedure may consist in manually rotating the footplate to produce sinusoidal stretch at a given speed, these methods may lead to a lack of consistent and regular mobilization velocity (Alhusaini et al. 2010; Moseley et al. 2001). For instance, angular velocity used to passively move the ankle joint ranged from 1°/s (Theis et al. 2016) to 60°/s (Alhusaini et al. 2010) and was different between children with CP (60°/s) and peers with TD (88°/s) in the study of Alhusaini et al. (2010). Even if EMG monitoring was commonly used to verify the absence of voluntary or reflex muscle contraction (which may be elicited by high angular velocity) (Alhusaini et al. 2010), higher passive joint stiffness is commonly observed when increasing angular velocity because of the visco-elastic characteristics of the musculo-tendinous unit (McNair et al. 2002). This was recently confirmed for Achilles tendon (AT) passive stiffness in both children with TD and those with CP (Theis et al. 2016).

Finally, the positioning of children, because of its impact on hip and knee joint angles, needs to be precisely defined since it strongly influences the results of ankle joint and plantarflexor muscles stiffness (Maïsetti et al. 2012). The knee joint angle must be accurately controlled given that the gastrocnemii muscles are in a slack position at a flexed knee angle (Maïsetti et al. 2012). This was not the case in the study by Ross et al. (20° to 40° of knee flexion) (Ross et al. 2011), potentially inducing a high variability in passive stiffness measurements. In the other reviewed studies, ankle joint passive stiffness was investigated with either the knee flexed (de Gooijer-van de Groep et al. 2013; Ross et al. 2011; Willerslev-Olsen et al. 2013) or extended (Alhusaini et al. 2010; Barber et al. 2011; Kruse et al. 2017; Tardieu et al. 1982; Theis et al. 2016). Besides the knee angle, the position of the hip may have an influence on the results. Non-muscular structures (i.e., fascia or nervous tissue such as the sciatic nerve) have been shown to limit the magnitude of ankle dorsiflexion (Nordez et al. 2017). For example, it has been reported that the ankle maximal DF angle is higher when the hip is in neutral position (i.e., 0°) compared to a more flexed position (i.e., 30°) (Andrade et al. 2016). Accordingly, the results of passive stiffness measurements may be different between the seated and the prone/supine position because the plantarflexor muscles are not the limiting factor when the hip is flexed and the knee extended. Although presenting an exhaustive presentation of the proper methodology to investigate joint passive stiffness through torque–angle relationships is beyond the scope of the present review (Magnusson 1998), the following guidelines can be proposed:

- *Material* Isokinetic dynamometers still appear as the "gold standard" devices to control angular velocities and joint positioning and should therefore be preferred to custom-made device. However, it may be argued that more adjustable devices are needed to better adjust to pediatric morphology (e.g., young children), and foot deformity (e.g., valgus/varus deformity, mid-foot break, etc.). Moreover, to further improve the capacity of clinicians to record data at the bedside of children with CP,

small and portable dynamometers have to be developed (Bénard et al. 2010).

- *Angular velocity* To avoid stretch reflex-induced contractions during lengthening of the PF muscles, the angular velocity must be very low. To counteract the impact of viscosity on passive stiffness and permit comparison between studies, angular velocities must be standardized. Referring to studies on healthy adults (Maïsetti et al. 2012) and children with CP (Theis et al. 2016), we suggest using an angular velocity of 2°/s.
- *Joint positioning* It should be accurately described according to its impact on muscle slack length. The stiffness of the triceps surae must be assessed both with the knee flexed, to stretch the soleus, and with the knee extended, to stretch the gastrocnemii. Because of the influence of non-muscular structures on the ankle passive range of motion (Nordez et al. 2017), the positions of the spine, pelvis, and hips should be controlled and set to neutral angles during the assessments. Moreover, the terminology used to describe ankle position should be explicitly described. For example, the term "neutral angle" may be quantified as 90° or 0°. In this current review, we defined the neutral angle as 0° (i.e., the anatomical position). Accordingly, we reported ankle angle values as positive for the dorsiflexion phase and negative for the plantarflexion phase.
- *Muscles conditioning* A number of passive loading/unloading cycles must be performed before the determination of passive joint/muscle stiffness (Maganaris 2003). Three (Theis et al. 2016) to five cycles (Maïsetti et al. 2012) of loading/unloading phases are commonly reported in the literature.
- *EMG monitoring* It is of utmost importance to record the EMG muscle activity of both the agonist (triceps surae) and antagonist (tibialis anterior) muscles during the stretching procedures to ensure that the muscles are in a passive state (Le Sant et al. 2019a). Muscle activity should be monitored live, but also checked post hoc, because of the difficulty to identify EMG activity from direct visual observation.
- *Methodology of data treatment* To discriminate between the origins of increased passive stiffness (i.e., shortening of PF muscles vs. altered mechanical properties), the slack angle or length has to be systematically measured. This may be performed for the ankle joint (Barber et al. 2011) or for a specific muscle using SWE (see below) (Le Sant et al. 2019b). This is a crucial point to limit the heterogeneity of passive stiffness outcomes reported in the literature.

Moreover, the choice of a similar and restricted range of ankle motion (e.g., 0° to 5° of DF) to compare children with TD and CP may not be representative of differences in mechanical properties, regardless of often limited maximal DF angles in children with CP (Ross et al. 2011). Altogether, we suggest that the slack angle and maximal DF angle should be systematically characterized and that passive stiffness should be calculated on the angular sector between the slack angle and 80% of maximal passive dorsiflexion, as involuntary muscle activity is known to occur past this 80% threshold (Mcnair et al. 2001). Considering the range between slack angle and 80% of maximal dorsiflexion provides information on both shortening and stiffness of the muscle tissue (Herbert et al. 2002; Le Sant et al. 2019b).

Regarding intrinsic factors, data from numerous works have contributed to an improvement in our understanding of the factors that influence the development of muscle stiffness in children with CP. Some discrepancies between studies may be explained by differences in the characteristics of the children samples. For instance, while most of the studies tested children with poor functional status [i.e., Gross Motor Function Classification System (GMFCS) III and IV], no difference in ankle joint passive stiffness between children with spastic CP and a better functional level (i.e., GMFCS I and II) and their peers with TD were found by Kruse et al. (2017). It is also important to notice that significant between-subject variability was observed in children with CP. For example, Willerslev-Olsen et al. (2013) reported that 20 children with spastic CP out of 35 presented with higher ankle joint passive stiffness, compared with the average stiffness reported in children with TD, while the remaining 15 children did not. Similarly, Ross et al. (2011) reported stiffness values to be lower than those of their peers with TD in 42% of children with CP (out of a sample of 121 children). Therefore, it appears that some children with CP present with increased stiffness, while others have normal or low stiffness values of their PF muscles. To give insight into this heterogeneity and into the pathophysiological mechanisms leading to the overall stiffness increase at the joint level, further investigation is needed. In the next section, we detail studies which investigated the muscle tissue and provided data about its architecture, morphology, and stiffness.

Passive muscle stiffness

At the muscle belly level

Tracking the musculo-tendinous junction using 2D ultrasonography during slow passive mobilization of the ankle may offer the opportunity to specifically estimate muscle and tendon stiffness during passive ankle DF (Cronin and Lichtwark 2013). Passive muscle stiffness is calculated in most studies as the slope of the muscle force–length curve, muscle force being estimated from the joint torque thanks

to motion analysis and muscle modeling (Theis et al. 2016), or mathematical regression (Kruse et al. 2017).

Such approaches have led to controversial findings. Theis et al. (2016) reported significantly higher passive GM stiffness in children with CP and a low functional level [mean age = 11.4 (3) years, GMFCS score III and IV] when compared to their peers with TD. Conversely, no differences in GM muscle passive stiffness between children with CP and good to fair locomotor function (GMFCS I and II) in children with TD were found in a later study (Kruse et al. 2017). Altogether, these results could support that GM increased stiffness may be linked to the severity of the motor impairment and/or activity limitations in children with CP.

It has been considered that greater resistance to passive muscle–tendon unit lengthening is provided by larger muscles (Gajdosik 2001; Willerslev-Olsen et al. 2018). Indeed, passive ankle joint stiffness has been shown to correlate with muscle size in healthy adults, and especially with muscle cross-sectional area (Ryan et al. 2009). Despite a lower GM growth rate (measured as GM volume), ankle joint passive stiffness (slope of the torque–angle curve) has been reported to increase significantly more with age in the first years of life in children with CP compared to their peers with TD (Willerslev-Olsen et al. 2018). In this study, conducted in children less than 4-year-old, the ankle range of motion remained similar between both groups and, thus, children with CP had not yet developed muscle contracture (Willerslev-Olsen et al. 2018). A significant reduction in muscle growth between children with TD and those with CP started around 12 months, while the significant increase in ankle joint stiffness in the CP group occurred much later (at about 27 months) (Willerslev-Olsen et al. 2018). The conclusions were that altered muscle growth precedes, and therefore might be a causative factor for increased stiffness in children with CP. Delayed onset of walking and altered gait were thought to impact muscle growth as a first step, through reduced loading and stretching forces applied to the muscles. It has to be kept in mind that during childhood and adolescence, 80% of the longitudinal lengthening of pennate muscles, such as the gastrocnemii muscles, is explained by hypertrophy of muscle fascicles (Bénard et al. 2011; Weide et al. 2015). An altered growth rate at the fascicle level may then lead to a lack of muscle belly length development. Thereafter, the discrepancy between bony and muscle growth has been considered as responsible for the secondary increase in muscle stiffness (Willerslev-Olsen et al. 2018).

The complexity of the instrumentation and data treatment in many of the aforementioned studies (muscle modeling, reconstruction of ultrasound images, mathematical regression) make this method inappropriate to assess muscle stiffness in daily clinical practice. Moreover, it should be acknowledged that muscle force is only estimated through

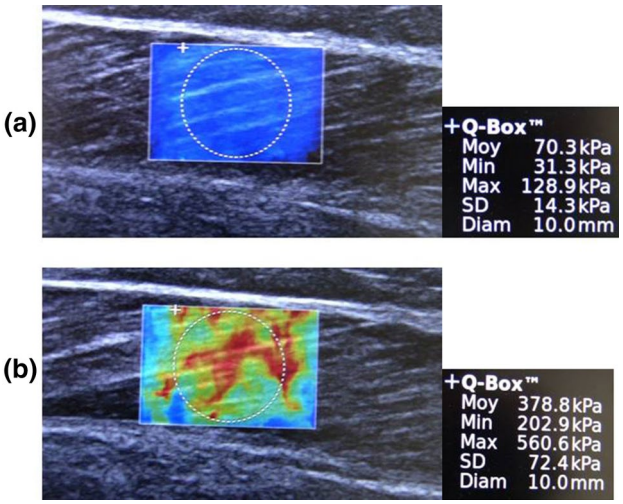

Fig. 3 Typical example of shear elastic modulus measurement on gastrocnemius medialis at two different muscle lengths (**a** − 20° of ankle plantarflexion **b** 20° of dorsiflexion) on the paretic leg in a child with unilateral CP. Personal data from our research team

models in these studies, and that the accuracy of such muscle passive stiffness measurement remains unclear.

Some limitations of the assessment of stiffness at the muscle level, such as the need for motion capture techniques synchronized with ultrasound data acquisition, may be overcome by the use of shear wave elastography (SWE). The basic principle of SWE is to use an acoustic radiation force impulse to create a shear stress within the investigated tissue, and then to map the induced distortion using ultrafast ultrasonography (Creze et al. 2018). This may provide real-time, quantitative and accurate imaging of passive muscle tension (Hug et al. 2015).

Briefly, measurements are made using an ultrasound probe to both induce and track shear wave propagation in a specific tissue such as a muscle. The velocity of the propagation of the shear wave is then recorded in a specific region of interest using ultrafast imaging and used to calculate the shear modulus, expressed in kPa (Fig. 3). The higher the passive muscle tension, the faster is the shear wave propagation and the greater is the shear modulus (or Young's modulus) (Hug et al. 2015; Lieber et al. 2017). Despite that skeletal muscle properties differ from those of an isotropic non-contractile tissue (e.g., liver, breast…) from which the rheologic fit model of SWE was issued (Creze et al. 2018), it was reported that the relationship between shear modulus and muscle length is linearly related to the passive force recorded during passive slow ankle joint mobilization (i.e., 2°/s) (Maïsetti et al. 2012). In addition, Nakamura et al. (2016) reported a strong correlation between GM musculotendinous junction displacement during slow lengthening and GM shear modulus. While the two latter studies were performed in healthy adults, an increase in shear wave speed

with increasing ankle joint, passive torque and fascicle strain has been reported using SWE in children with CP (Brandenburg et al. 2016; Lee et al. 2016). Therefore, as the shear modulus assessed through SWE is a valid measure of passive muscle tension, its relationship to muscle lengthening is consistent with the definition of muscle stiffness.

Altogether, it is well acknowledged that muscle shear modulus may be used to estimate passive tension during stretching in humans (Hug et al. 2015). Although the reliability of shear modulus measurement has been established at rest (Lacourpaille et al. 2012; Nakamura et al. 2016) or during slow passive stretching (Maïsetti et al. 2012) in healthy adults, it remains however to be determined in children with TD and those with CP.

Using elastography, increased shear wave velocity has been reported for the GM (Bilgici et al. 2018; Kwon et al. 2012), gastrocnemius lateralis (GL) (Brandenburg et al. 2016) and soleus muscles (Kwon et al. 2012; Vola et al. 2018) in children with spastic unilateral and bilateral CP, when compared to their peers with TD. Moreover, when comparing paretic and non-paretic limbs in children with unilateral CP, Lee et al. (2016) reported greater GM shear wave velocity in the paretic limb, when assessed in the neutral ankle dorsiflexion position (i.e., 0°).

In particular, higher shear wave velocity for the GM muscle was reported in 9-year-old (Bilgici et al. 2018) and in 5-year-old children with CP (Kwon et al. 2012), when compared to age-matched children with TD. In many of these studies, children were positioned prone with the feet over the edge of the examination table without any control of the ankle angle (Bilgici et al. 2018; Kwon et al. 2012; Vola et al. 2018). The ankle joint position in these studies is the consequence of the action of the gravity on the ankle, which is influenced by the positions of the hip and knee, and on the body orientation (prone or supine). Such positioning does not enable the investigators to have information on joint angle nor on moments, which adds variability in the measurements (as discussed above for torque–angle curves) and then limits the interpretation of these data. Measurements were performed in a single resting position, and cannot provide detailed information about the stiffness of the GM, which would require assessing shear wave velocity–ankle angle relationships, as was recently performed in adult stroke patients (Le Sant et al. 2019b). Once more, potential associated shortening appears to be a confounding factor when assessing muscle stiffness. SWE measurements were often performed without an accurate control of the ankle position and as a consequence of the muscle length (Bilgici et al. 2018; Kwon et al. 2012; Vola et al. 2018). Furthermore, studies reporting shear wave velocity at a fixed ankle angle did not investigate the slack angle of the ankle, nor the slack length of the GM muscle (Brandenburg et al. 2016; Lee

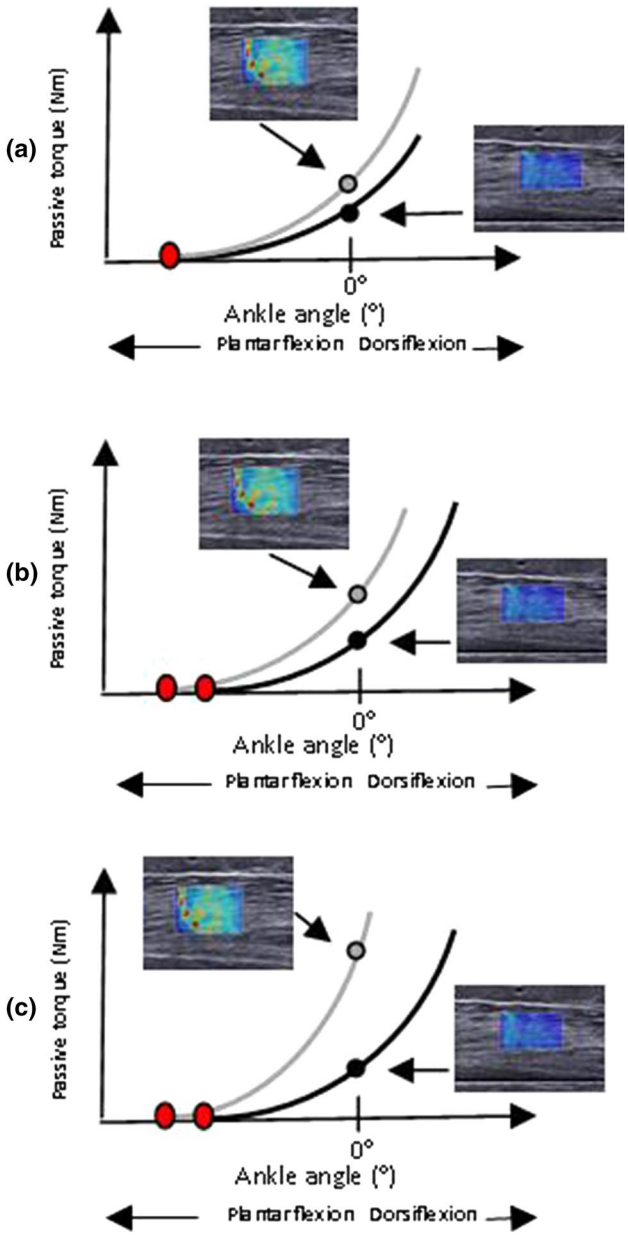

Fig. 4 Examples of SWE measurement interpretation at common angle (neutral angle: 0°) according to torque–angle curve relationship in children with TD (black lines) and children with CP (gray lines). Ankle angle was represented by the angle between the tibia and the foot sole. Slack angle is represented by a red circle. Higher shear elastic modulus measurement in children with CP (gray line) compared to peers with TD (black line) may be indicative of higher GM muscle passive stiffness (**a**), PF muscles shortening (**b**) or common presence of both phenomena (**c**) according to differences in slack and maximal DF angle, compared to children with TD. Torque–angle curve were obtained based on outcomes from the literature in healthy adults and in children with CP (Barber et al. 2011; Tardieu et al. 1982)

et al. 2016), while significant differences in maximal DF angle and slack angle/length may be present (Brandenburg et al. 2016). As a consequence, the findings in these works could be the result of shortening of the PF muscles on the paretic side relative to the non-paretic side in children with unilateral CP or to legs of their peers with TD (Barrett and Lichtwark 2010; Kruse et al. 2018) rather than increased stiffness, as defined in the first paragraph of this review (Fig. 4).

For instance, although higher absolute shear wave velocity values were found in the GL muscle in children with CP compared to their peers with TD at different ankle angles (i.e., 20°, 10° and 0° of plantarflexion), the increasing rate of the shear modulus value (i.e., stiffness, as previously defined) was similar between both groups (Brandenburg et al. 2016). However, values for children with CP presenting high variability and measurements were not taken at maximal DF angles (i.e., 4° and 12° for children with CP and their peers with TD, respectively). More studies investigating SWE in the PF muscles on the whole range of passive dorsiflexion are needed to confirm increased muscle stiffness and to precisely determine its distribution. To date, only one study has investigated shear wave velocity according to the different PF muscles, and the alteration was reported to be greater for the GM than for the soleus muscle (Kwon et al. 2012). The recent findings of Le Sant et al. (2019b) displayed that, in stroke patients, increased muscle tension (assessed through SWE) is highly dependent on the muscle and even on the muscle region (increased tension in the distal parts of soleus, GM, and GL, relative to their proximal parts), suggesting a necessity to perform such stiffness mapping in children with CP as well.

At the Achilles tendon level

As for the muscle, the stiffness of the AT can be investigated by tracking the musculo-tendinous junction during passive mobilization. AT stiffness may be determined as the slope of the AT force–length curve, AT force being calculated by dividing ankle torque by AT moment arm (Kruse et al. 2017), i.e., the distance between the malleolus lateralis and the action line of the tendon (Konrad and Tilp 2014).

Despite known altered morphological properties, AT passive stiffness in children with CP has been poorly investigated. Theis et al. (2016) did not find any significant alteration in AT passive stiffness in children with CP, while Kruse et al. (2017) reported significantly decreased AT passive stiffness. Discrepancies between studies may be explained by differences in the range of torque used to calculate the slope of the AT force–length curve. Conversely, both studies demonstrated no difference between children with CP and TD in AT Young's modulus (i.e., stress/strain, a measure of intrinsic stiffness not influenced by AT morphology). This suggests that AT mechanical properties were not altered, despite AT having been described as longer and thinner in children with CP compared to children with TD (Gao et al. 2009; Theis et al. 2016).

Interestingly, Theis et al. (2016) found a significant increase in muscle to tendon stiffness ratio in their sample of children with CP when compared to peers with TD. This result was corroborated by higher AT/GM muscle lengthening ratio (range 0.86–1) in children with CP compared to children with TD (range 0.53–0.64) during ankle mobilization towards dorsiflexion (Kalkman et al. 2018a).

In summary, there is conflicting evidence on whether stiffness of the AT is reduced, or unchanged, in children with CP. While SWE has been used to assess AT stiffness in healthy humans (DeWall et al. 2014; Suydam et al. 2015), no data are available in children with CP.

At the fascicle level

Inconsistent data on muscle fascicle length in the plantarflexors were reported in children with CP. Some authors found significantly decreased fascicle length (Matthiasdottir et al. 2014; Mohagheghi et al. 2007) contrary to others (Malaiya et al. 2007; Shortland et al. 2007). Such discrepancies may be due to the ankle angle at which the measurements were made. If performed at a common angle between subjects with CP and TD, while overall muscle length was likely different due to shortening, a possible strain could have been induced in children with CP. In keeping with our introducing position on the proper definition of stiffness, we believe that dynamic studies, assessing the lengthening of the fascicles during stretching, are more appropriate to determine their stiffness. This lengthening capacity of GM muscle fascicles during stretching has indeed been investigated. Contradictory results were found regarding fascicle lengthening and fascicle passive stiffness (slope of the torque–fascicle length curve) in young adults and children with CP compared to peers with TD during passive stretching. Barber et al. (2011) displayed reduced fascicle lengthening during stretching, while Matthiasdottir et al. (2014) found that muscle fascicles were shortened at rest, but much more lengthened by stretching, in children with CP. Such differences may be related to differences in methodology and characteristics of participants. Using a rigorous approach, a recent study reported a significant reduction in lengthening of fascicles in the GM during passive stretching in children with CP compared to peers with TD (Kalkman et al. 2018a). Therefore, in summary, despite a lack of studies dealing with fascicles alterations in CP muscles and no clear consensus, it seems that children with CP present reduced GM fascicles lengthening capacity and increased fascicle stiffness.

At the sarcomere level

GM fascicles lengthening and stiffness may be better understood by investigating the properties of the sarcomeres, which are the basic units of muscle fibers. Mathewson et al. (2014) performed biopsies on the soleus and gastrocnemii muscles in 11.1 (±5.1)-year-old children with CP undergoing muscle–tendon unit lengthening as a treatment of equinus contracture. Sarcomere lengths were measured using laser diffraction, and stress/length curves were established to calculate tangent stiffness. Increased sarcomere length at rest was reported, together with increased stiffness of both fibers [i.e., without extracellular matrix (ECM)] and fascicles (i.e., including ECM) in children with CP compared to healthy adults (Mathewson et al. 2014). Interestingly, in children with CP, fibers and fascicles had similar stiffness, contrary to healthy adults in which fascicles were stiffer than isolated fibers (Mathewson et al. 2014). Taken together, increased passive stiffness, measured in vivo and in vitro at fascicles and fibers level (torque–length curve), seems related to the longer in vivo resting sarcomere length reported in spastic muscles compared to controls (Mathewson et al. 2014; Smith et al. 2011). Overlengthened sarcomeres (i.e., with increased length, compared to controls) in PF muscles may be a response to a mismatch between skeletal bone and muscle growth during childhood in children with spastic CP (Pingel et al. 2017).

Interestingly, findings reported for PF muscles in children with CP did not appear to be generalizable to other muscular groups. Firstly, Smith et al. (2011) reported no significant change in the passive stiffness of muscle fibers in spastic hamstrings, compared to muscles from control subjects, which contrasts with the PF muscles. Secondly, overlengthened sarcomeres did not appear systematically related to muscle contracture in CP. For example, reduced wrist extension was not related to increased sarcomere length in spastic flexor carpi ulnaris muscles (Smeulders et al. 2004). Some factors could contribute to these discrepancies. For example, differences between muscles regarding the amount and organization of collagen has been reported (Booth et al. 2007; Smith et al. 2011). In addition, the distribution of sarcomere length within muscles fibers resulting from myofascial load transmission and from the muscle macroscopic architecture may potentially lead to variability in findings (Dayanidhi et al. 2015; Yucesoy and Huijing 2007). Taken together, the morphological and mechanical properties at the sarcomere level appear to vary according to the muscle in children with CP. However, data in this field of research remain scarce and controlled studies are almost impossible, given that invasive procedures are required. To increase knowledge on the mechanisms leading to sarcomeres overlengthening, histological outcomes are needed. Surgical interventions, especially multilevel procedures, performed to correct contractures in children and teenagers with spastic CP, may offer this opportunity.

At the muscle fiber and extracellular matrix level

Overlengthened sarcomeres may be related to altered sarcomerogenesis. Longitudinal and cross-sectional postnatal muscle growth, and indeed in-series sarcomeres addition, are related to activation and self-renewal of satellite cells, i.e., quiescent stem cell located in the periphery of the muscle fiber, outside the sarcolemma (Dayanidhi et al. 2015).

A depletion in satellite cells (Dayanidhi et al. 2015; Smith et al. 2013) and altered myogenic potential (i.e., capacity to fuse and to produce myotubes) (Domenighetti et al. 2018) were reported in spastic muscles of children with CP. As a result, this may lead to a lack of in-series sarcomere addition during growth (Gajdosik 2001; Martín Lorenzo et al. 2017).

At the sarcomere level, regarding the structural proteins of the muscle fibers, increased tension in response to stretching may be related to alterations in components, such as:

- Cross-links between actin and myosin myofilaments;
- titin (a major component of the endo-sarcomeric cytoskeleton) and its elastic properties; and
- desmin proteins, which contribute to the exo-sarcomeric cystoskeleton

Both titin and desmin are known to be stretched while the sarcomere lengthens (Gajdosik 2001). The titin protein has been suspected to influence passive stiffness given its major size and weight. However, experimental measurement performed in children with CP for PF muscles did not seem to support that alterations in titin contribute to the increase in stiffness (Mathewson et al. 2014). Titin mass was reported to be slightly greater in children with CP compared to peers with TD, whereas increased stiffness is typically associated with smaller titin mass (Mathewson et al. 2014). Similar conclusions have been drawn for the hamstring muscles in children with CP (Smith et al. 2011). Other non-identified basic structural proteins of the muscle fiber are therefore likely to be involved in the increase of muscle stiffness.

In addition, it has been hypothesized that the ECM may be less organized and less able to resist force in children with CP (Mathewson et al. 2014). Interestingly, in the latter study, there was no difference in collagen content in both soleus and gastrocnemii muscles between subjects with CP and TD, contrary to previous findings in other muscles such as vastus lateralis (Booth et al. 2007) or hamstrings (Smith et al. 2011). Therefore, rather than alterations in proteins, the architectural organization of the ECM would be altered, which may lead to the increase in muscle stiffness. Pingel and Suhr (2017) highlighted that the function of the ECM is not fully identified, and its relevance to stiffness remains

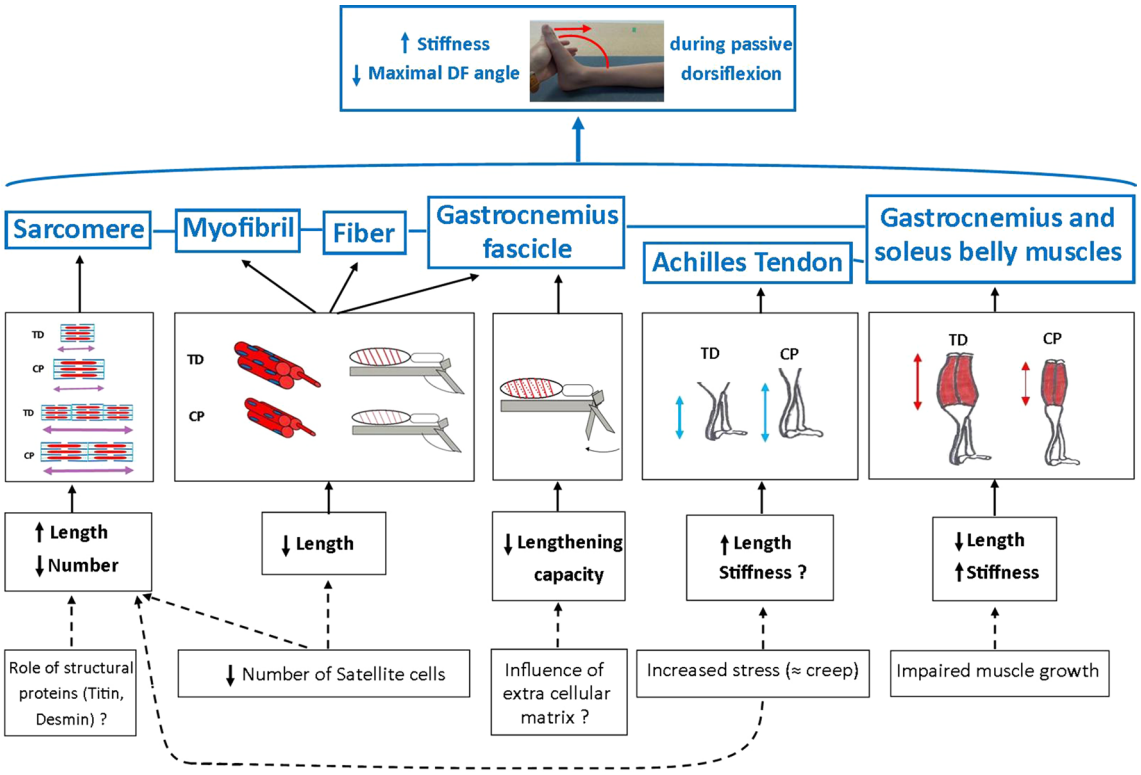

Fig. 5 Conceptual relationship diagram illustrating in children with cerebral palsy alterations from the sarcomere to the joint level that may lead.to decreased range of motion and increased passive stiffness. Known and hypothetical relationships between the pathological features reported in the literature at each of these levels are represented by full and dotted arrows, respectively

unclear. ECM, however, plays a fundamental role in muscle integrity and homeostasis regulation. For instance, contractile forces are laterally transmitted from the sarcomeres across the sarcolemma to the ECM by mechano-sensitive structures such as costameres (Pingel and Suhr 2017). More studies are needed to increase our understanding of the role of the ECM in muscle mechanical properties. More generally, studies in the upper limb in children with CP suggest that muscle contractures may also be related to alterations in the connective tissue. For instance, myofascial load transmission induced by neurovascular tracts (extramuscular myofascial force transmission) or force transmission between the linked intramuscular stromata of two adjacent muscles (intermuscular myofascial force transmission) have been displayed (de Bruin et al. 2014; Huijing 2007; Smeulders and Kreulen 2006).

Summary

The interpretation of passive stiffness measurements is highly influenced by the methodological approach, the data treatment, and the characteristics of the population. Ideally, SWE and dynamometry measurements may be preferentially performed on the whole range of motion, combined with slack angle and length assessments. This would allow to take muscle shortening into account, and then to accurately consider the maximal DF angle, or merely 80% of this angle. Consequently, the slope of the torque–angle curve and shear elastic modulus have to be determined on a similar range of motion or torque from slack angle/length.

Increased stiffness of the PF muscles may be considered as a primary contributor to increased stiffness at the overall ankle joint level (Fig. 5). However, there are still few studies that investigated the other elements of the whole PF complex. The mechanical properties of muscles other than the gastrocnemii and soleus and of the AT may be considered more accurately. Similarly, further longitudinal studies are needed to understand the links between the impairments reported at the macro- and microscopic levels (Fig. 5). The depletion of satellite cells may be related to altered muscle growth and sarcomerogenesis. However, the direction of the cause–consequence relationship remains unclear. Similarly, overlengthened sarcomeres may be induced by a decreased PF muscle lengthening reported during growth. Yet, whether it really plays a precursor role or not in the increased passive stiffness remains to be elucidated. Nonetheless, better elucidating the pathophysiology of spastic muscles in children

with CP is crucial in an attempt to further optimize therapeutic strategies.

Clinical application

Decreasing muscle passive tension and stiffness is a common goal of physical therapy in neurological diseases. This may prevent the development of contracture and favor the active motion of the antagonist. The literature provides some results on the influence of therapeutic interventions on both morphological and mechanical properties of spastic PF muscles in children with CP. Yet, available studies remain scarce. For example, it has been reported that passive stretching therapy may increase gastrocnemius belly and fascicles length, despite no clear effect on ankle joint passive stiffness (Kalkman et al. 2018b; Theis et al. 2013, 2015). Botulinum toxin injections may decrease gastrocnemius passive tension at a given angle (Brandenburg et al. 2018; Ceyhan Bilgici et al. 2018; Park and Kwon 2012), but have no effects on ankle joint passive stiffness (Alhusaini et al. 2011). In some cases, adverse effects have even been described (e.g., decreased muscle volume after botulinum toxin injection, Alexander et al. 2018; increase AT length after castings, Peeters et al. 2018). Furthermore, the effectiveness of more recent strategies of physical treatment, such as neuromuscular electrical stimulation (Damiano et al. 2013; Pool et al. 2016), intensive strengthening (Gillett et al. 2016) or gait training (Willerslev-Olsen et al. 2014), to improve morphological and mechanical muscle properties have been described.

While presenting an exhaustive synthesis of the field of research on therapeutic interventions in children with CP was beyond the scope of the present review, it is clear that providing a sufficient body of knowledge about the impact of long-term therapeutic interventions targeting muscle stiffness and contracture performed during growth in children with CP now appears urgent. We hope this would be possible now that the heterogeneity of the measurement methods and of the population characteristics have been clearly displayed in the present review. In that line, the clear guidelines that we provided can serve as a future framework for these therapeutic studies.

Conclusion

The present review highlights the variability of the methods found in the literature to assess the stiffness of the PF muscles in children with CP. This makes the comparison between studies difficult and explains why knowledge about the importance, spatial, and temporal distribution of increased stiffness among the plantarflexor muscles in this population remains incomplete. Shortening of the PF muscles appeared to be a major confounding factor in many studies. The need for consistency in the assessment stands for both research and potential clinical application. The term "stiffness" should now be rid of any ambiguity or variability in its use. Besides methodological issues, an important heterogeneity of PF muscle stiffness in children with CP appears to be a major statement of this review. While the precise determining factors of this variability remain to be discovered, this emphasizes that passive stiffness should be assessed at the individual level before treatment options are considered. We therefore wish to stress two points that are crucial for the application of stiffness measurements: standardization of the protocol used, including slack and maximal dorsiflexion angle/length measurements, and individualized assessment. Indeed, measuring passive stiffness of the ankle joint and PF muscles is of high interest in children with CP, given the high incidence of contracture and equinus gait development during growth in this population. This may be complementary to range of motion, spasticity, and gait assessments, and could be measured in daily clinical routine in the future to provide further knowledge on mechanical properties during follow-up. To do so, easy-to-use portable devices are mandatory, and a standardized protocol must be established.

Distinguishing stiffness form shortening can be challenging, but is key to understanding the development of hyperresistance and contracture during growth. Associated with mechanical properties, morphological measurement, such as gastrocnemius and/or AT tendon length, may further permit to clarify the pathophysiology of contracture in research. SWE is a promising tool for assessing stiffness, compatible with the classical methods (dynamometry) and easily convertible to B-mode ultrasound. This may allow the evaluation of muscle morphology, such as gastrocnemius and/or AT tendon length, together with mechanical properties. It may further permit the clarification of the pathophysiology of contracture and help clinicians and researchers to design non-surgical treatments to relieve or even prevent this impairment.

Yet, many issues still need clarification. What is the pathophysiology of increased passive stiffness at the joint, muscle, fascicle, and fibers level and its link with altered muscle growth rate during childhood? What is the time course of the alteration of muscle structure during growth at the sarcomere level? Can changes in passive stiffness be induced by therapeutic interventions and impact clinical impairments, gait, and posture?

We hope that this review displayed the evidence for the gray areas in this topic, and that it will help future research focusing on musculoskeletal impairments, to the benefit of children with CP.

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Compliance with ethical standards

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

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