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# Assessing muscle architecture with ultrasound: implications for spasticity

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***Abstract***

Botulinum Neurotoxin Type A (BoNT-A) injections using Ultrasound (US) guidance have led to research evaluating changes in muscle architecture. Controversy remains as to what constitutes increased Echo-Intensity (EI) in spastic muscles and whether this may affect outcomes. We aim to provide a narrative review of US muscle architecture changes following Central Nervous System (CNS) lesions and explore their relationship to spasticity. Medline, CINAHL, and Embase databases were searched with keywords: ultrasonography, hypertonia, spasticity, fibrosis, and Heckmatt. Three physicians reviewed the results of the search to select relevant papers. Reviews identified in the search were used as a resource to identify additional studies. A total of 68 papers were included. Four themes were identified, including histopathological changes in spastic muscle, effects of BoNT-A on the muscle structure, available US modalities to assess the muscle, and utility of US assessment in clinical spasticity. Histopathological studies revealed atrophic and fibro-fatty changes after CNS lesions. Several papers described BoNT-A injections contributing to those modifications. These changes translated to increased EI. The exact significance of increased muscle EI remains unclear. The Modified Heckmatt Scale (MHS) is a validated tool for grading muscle EI in spasticity. The use of the US may be an important tool to assess muscle architecture changes in spasticity and improve spasticity management. Treatment algorithms may be developed based on the degree of EI. Further research is needed to determine the incidence and impact of these EI changes in spastic muscles.

**Key Words:** botulinum neurotoxin; echo-intensity; Modified Heckmatt Scale; muscle spasticity; muscle fibrosis; ultrasound.

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Our understanding of spasticity has evolved in recent decades. The numerous definitions of this complex phenomenon often focus on neural structures and processes,[1-4] but the transformation occurring in spastic muscles and soft tissues adds further complexity and is even less understood.

Histological and imaging methods have shown spasticity and chronic disuse to be associated with greater variability in muscle fiber size and type, as well as a proliferation of disorganized extracellular matrix material, increased fat content, muscle shortening, atrophy, and sarcopenia, potentially leading to muscle stiffness and contractures.[5-8] The umbrella term *muscle fibrosis* is often used to refer to these changes, but controversy remains as to what constitutes fibrosis.[7,8]

With the increasing use of US guidance for chemodenervation,[10-11] the US may also serve as a reliable tool to assess spastic muscle and its evolution over time.[12] In neuromuscular disease, fibrofatty infiltrations correspond to increased EI.[13-14] In spasticity, muscle fibrosis is often considered a potential cause of treatment failure.[15] Muscle and soft tissues are often targeted by different spasticity treatments.[16] Thus, further elucidating the relationship between muscle changes and spasticity manifestation may better inform treatment.

This paper aims to provide a narrative review of muscle

architecture changes following CNS lesions, describe their relationship to spasticity, and explore the potential role of the US in muscle evaluation to suggest areas of future research. This is the first review to synthesize evidence of spastic muscle changes and to highlight the utility of the US (beyond targeting) for investigating often overlooked peripheral phenomena in spasticity research and clinics.

## Materials and Methods

A literature search was performed by the College of Physicians and Surgeons of British Columbia librarians for related articles published between 1986 and March 2022, using Medline, CINAHL, and Embase databases. The five-stage methodological framework of Arksey and O'Malley was followed. The research question was the following: "What muscle architectural changes are seen in spasticity and how can these changes be evaluated using ultrasound?". Keywords used were: ultrasonography, muscle tonus, hypertonia, spasticity, fibrosis, and Heckmatt. Three physicians independently reviewed the results of the search at title, abstract, and full text. Reviews identified in the search were used as a resource to identify additional individual studies. Following this, reference lists of full text and a hand search of Google Scholar was performed which also included relevant French and Italian literature. Inclusion criteria were: i) any level of evidence, ii) studies conducted on animals and/or humans, iii) studies reporting muscle architecture/histology changes post-CNS lesions, and/or effects of BoNT-A on the muscle structure, and/or use of US in spasticity evaluation, and iv) full-text available for review. One reviewer independently extracted relevant data from included articles and recorded data in a spreadsheet. Demographic information included author, year of publication, sample size, study design, level of evidence, patient diagnoses, muscle architectural changes, and US changes. The level of evidence was recorded as provided by the study (Supplementary Material, Table 1).

## Results

Sixty-eight papers were included in this review (Supplementary Material, Table 1). Studies were published from 1986 to 2021. Most studies were of Level III Evidence (N= 41), followed by Level V (N=9), Level IV (N=7), Level II (N=2), and Animal Studies (N=7). Four themes were identified, including histopathological changes in spastic muscle, effects of BoNT-A on the muscle structure, available US modalities to assess the muscle, and utility of US assessment in clinical spasticity.

### *Histological changes in spastic muscle*

In peripheral nervous system disease, a strong correlation between the extent of nerve damage and the degree of muscle pathology was found in horses with laryngeal hemiplegia (Table 1).[17] Affected laryngeal muscles also showed extensive atrophy and fiber-type grouping, indicative of denervation and reinnervation.[18] In horses affected by Australian Stringhalt, abnormally wide distribution in fiber size and a reduction in type II fibers were observed as a consequence of distal axonopathy.[19] Following transection of the recurrent laryngeal nerve, echogenicity of affected laryngeal muscles increased significantly over time compared to the side with no neurectomy.[20] However, Pillen *et al.* showed that although the calculation of mean muscle EI strongly correlates with structural muscle changes and the severity of muscle pathology, it is impossible to know whether an increased EI has resulted from fibrosis, fatty infiltration, or both without a complementary muscle biopsy.[21] Other variables, such as overlying skin and superficial fascia superposition, can also interfere with muscle EI.[21]

Structural and functional changes also occur following CNS lesions. Lieber et al.'s work on rats with spinal cord transection demonstrated long-term changes in muscle contractile properties affecting slow muscles to a greater extent compared to predominately fast muscle, with slow-to-fast fiber type conversion associated with a decrease in cross-sectional area and an increase in contractile speed and specific tension.[22,23] The morphometric properties of muscles are also altered, with fiber atrophy and an increased proportion of endomysial and perimysial connective tissue in both slow and fast muscle.[23,24]

In human subjects, previous studies revealed a significant positive correlation between collagen type I accumulation in thickened endomysium, decrease in fiber cross-sectional area, and more severe muscle stiffness in children with spastic cerebral palsy.[25,26] Though these muscles are stiffer,[26,27] the bundles are more mechanically fragile with more disorganized, low-quality extracellular material.[28] Further structural changes include loss of sarcomeres, increase in the ratio of collagen to muscle fiber, increase in fat content within muscles and tendons, and shortening of muscle fibers with decreased passive extension capacity.[5-7] Concerning sarcomere length and fiber type conversion, results are more heterogeneous and hardly predictable, emphasizing the complex character of spastic muscle in human subjects.[26-29] Other crucial unanswered questions remain regarding the role of extracellular matrix adaptation[30] and hyaluronan accumulation[31] in reduced range of motion and stiffness, the intrinsic and extrinsic factors influencing those changes, the influence of genetics and epigenetics, and the limitations of current methods to quantify and understand muscle rheological properties and architectural transformation.[29,32]

### *Effects of BoNT-A on the muscle structure*

Concerning extrinsic factors potentially affecting muscle structure and biomechanical properties, BoNT-A injections are suspected to have lasting effects that must be considered (Table 2).[33] Mathevon *et al.* conducted a systematic review of the effects of BoNT-A injections in animals and humans. They found that in animals, a single injection of BoNT-A induced muscle atrophy that was still incompletely recovered at one year. After one injection, the percentage of fast type IIb fibers decreased in favor of intermediate type IIa fibers and slow type I fibers. With monthly injections, the number of myosin-heavy chains associated with faster phenotypes decreased after the third

month.[33] In humans, neurogenic atrophy compensated by fibrosis was also noted, but in only one study.[34] The lack of standardized measurement procedures for assessing the architectural consequences of BoNT-A injections on muscles with 2D US was outlined.[33]

A prospective histopathologic study by Valentine *et al.* on ten ambulatory children with cerebral palsy also confirmed a positive association between BoNT-A injections and neurogenic atrophy between four months and three years after the last treatment.[35] Regarding the BoNT-A effect on the different muscle fiber types, they showed a slow type I fiber loss and a fast type II fiber predominance significantly related to the number of treatments of BoNT-A. It is however worth mentioning that the distinction between type IIa and IIb fibers was not made by Valentine's group. It remains that the histopathological outcome of post-BoNT-A treated human muscle is variable.

In 2020, Picelli *et al.* investigated the clinical and US architectural changes induced by BoNT-A in 21 post-stroke patients with spastic equinus.[36] At four weeks post-injection, they did not observe any significant effect of BoNT-A treatment on ultrasonographic characteristics (EI, muscle thickness, and pennation angle).

In 2021, Battaglia *et al.* investigated the effects of BoNT-A by conducting a cross-sectional observational study on 53 spastic hemiparetic stroke survivors.[37] They concluded that BoNT-A does not seem to influence muscle degeneration and that EI increase appears to be primarily related to spastic muscle evolution and functional impairment. Interestingly, in subjects with preserved walking capability and lower spasticity grade, an increase in EI of the medial gastrocnemius was observed in the paretic limb alone, but in patients with impaired gait and more severe spasticity, similar US changes were observed in both calves.



***Table 1.*** *Changes in muscle histology.*

| First Author, Date | Population | Change in Muscle Histology |
|---|---|---|
| Booth, 2001 | Pediatric (26, mean age 10.6 years)<br>Diplegic or quadriplegic cerebral palsy | Increased collagen accumulation in spastic muscle endomysium |
| Cahill, 1986 | Animal - Equine (15 horses)<br>Laryngeal hemiplegia | Muscle damage reflects nerve damage present |
| Chalmers, 2015 | Animal - Equine (28 horses)<br>Recurrent laryngeal nerve transection | Increased echo intensity of muscle on ultrasound |
| Friden, 2003 | Adult (41 control without neuromuscular condition)<br>Pediatric (15 experimental)<br>Cerebral palsy | Muscle fibers developed passive tension at shorter sarcomere length |
| Harrison, 1991 | Equine (18 foals)<br>Equine recurrent laryngeal neuropathy | Muscle fiber grouping<br>Neurogenic atrophy |
| Lieber, 1986 | Animal - Rats (24, 10 experimental, 14 control)<br>Thoracic spinal cord transection | Slow to fast fiber transformation<br>Slow muscle less able to generate prolonged contractionIncreased type 1 fiber atrophy |
| Lieber, 2003 | Adult (21 control without neuromuscular condition)<br>Pediatric (9 experimental)<br>Cerebral palsy | Muscle cells stiffer but extra-cellular matrix of inferior mechanical strength |
| Pillen, 2009 | Animal (14 golden retrievers)<br>Muscular dystrophy | Increased intersitial fibrous tissue correlated with increase echo intensity on ultrasound |
| Slocombe, 1981 | Animal - Equine (9 horses)<br>Australian Stringhalt | Increased type I fibers<br>Loss of type II fibers |
| Smith, 2011 | Pediatric (33 experimental, 19 control)<br>Cerebral palsy | Muscle bundles including extra-cellular matrix stiffer |

***Table 2.*** *Change in muscle structure with botulinum neurotoxin A (BoNT-A).*

| First Author, Date | Population | Intervention | Assessment | Change in Muscle Structure with BoNT-A |
|---|---|---|---|---|
| Battaglia, 2021 | 53 patients with spastic hemiparesis following stroke | Patients had received toxin (dosing not reported), mean treatment cycles 6 (range 4-8). Time of stroke to first treatment mean 1.1 years | Structural ultrasonographic differences between medial gastrocnemius and soleus in affected and unaffected limb. Assessed: cross sectional area, muscle thickness, pennation angle and mean gray value | • No relevant influence of BoNT-A in contributing to tissue degeneration in spastic muscles |
| Mathevon, 2015 | Systematic review of 21 articles (involving humans and animals) | | Muscle measures (N=9) – balance, optical microscopy, histochemistry; Imaging (N=10) – B-mode ultrasound, MRI, elastography; Biomechanical measurements (N=3) – passive torque | • Muscle atrophy<br>• Reduction in muscle thickness<br>• Reduced pennation angle<br>• Decreased fast type IIb fibers in favour of type IIa/slow type I<br>• Myosin heavy chains reduced |
| Picelli, 2020 | 21 chronic stroke patients | BoNT-A injection into affected gastrocnemius medialis and lateralis (dose not reported) | Ultrasonographic characteristics at one-month post-injection (*i.e.* Muscle echo, thickness, pennation angle, achilles tendon thickness and hardness) | • No significant effect of BoNT-A injection on ultrasound characteristics |
| Schroeder, 2009 | Two healthy adult male volunteers (47 and 31 years) | Single dose 74 units to lateral gastrocnemius (3 sites/muscle), Saline of 2 m: into contralateral limb lateral gastrocenmius | MRI imaging at 3, 6, 9 and 12 months after injection; Signal intensity alternations, cross-sectional area; Histopathology; Electron microscopy | • Denervation of neuromuscular junction on electron microscopy<br>• High signal intensity pattern on STIR sequence in injected muscles persistent at 12 months post-injection.<br>• Neurogenic fiber atrophy with some compensatory fiber hypertrophy |
| Valentine, 2015 | 10 patients with cerebral palsy (mean age 11.6 years) | Onabotulinum toxin in 2-4 sites *per* gastrocnemius muscle | Open muscle biopsy from medial gastrocnemius and vastus lateralis (control) | • Neurogenic atrophy in medial gastroscnemius between 4 months to 3 years post BoNT-A<br>• Type I fiber loss with type II predominance |

### *Available ultrasound modalities for muscle assessment*

The US has become a popular tool that has risen to fulfill the need for a more reliable and accessible method to assess spastic muscle and its evolution over time (Table 3).[12] Three main US modalities have been used to study spastic muscles: morphological changes,[36-52] sonoelastography,[36,38,43,45,47,51,53-65] and echogenicity.[36,37,44,49,52,66-71]

#### *Morphological changes*

Morphological changes observable with the 2D US include muscle thickness, pennation angle, and muscle depth. Assessing morphological changes is a more conventional approach and can provide useful information about the properties of the muscle fascicle.[46] Given the high variability of each parameter, there are no established reference values, and the collected information requires manipulations to be interpreted.[36,38-52,72]

#### *Sonoelastography*

Sonoelastography provides information about tissue stiffness.[73,74] It may be used to estimate muscle strain qualitatively[47,51,53-57] or quantitatively with shear wave elastography.[36,38,43,45,54,58-63] A systematic review and meta-analysis reported that US elastography has moderate reliability when used in neurological populations.[74] Moreover, its usage requires expensive software, and highly qualified technicians, and does not assess muscle echotexture when we know there is growing interest regarding differentiation of EI.[67,68]

#### *Echogenicity*

Interestingly, a strong correlation was found between elastography and EI in stroke-impaired muscles.[75] Echogenicity can also be assessed qualitatively[36,44,49,67-71,76] or quantitatively with software-generated gray-scale score and pixel analysis.[37,41,52,61,69,75] Brightness or B-mode US can be used to visualize tissues with varying sonoacoustic properties; these properties in turn determine the number of echoes returning to the transducer. Structures will appear bright or hyperechoic when they are highly reflective of sound waves, whereas they will appear dark or hypoechoic when they reflect few sound waves to the transducer. In the US, skeletal muscle appears as a mix of hypoechoic contractile fascicles and hyperechoic intramuscular connective tissue. By altering the histopathological properties of muscle, spasticity also alters its solo acoustic features, presumably due to atrophy and fibro-fatty hyperechoic replacement of hypoechoic contractile elements.[10] However, coexisting variables such as aging, muscle strength, and sarcopenia can also influence EI.[77-80]

Like all medical imaging modalities, US images exhibit

***Table 3.*** *Available US modalities for muscle assessment.*

| Morphological Changes | Sonoelastrophy | Echogenity |
|---|---|---|
| • Muscle thickness<br>• Pennation angle<br>• Muscle depth | • Muscle strain<br>• Shear wave elastrography | • Gray scale score<br>• Pixel analysis<br>• Brightness |
| Battaglia, 2021 | Askin, 2017 | Battaglia, 2021 |
| Calvo-Lobo, 2018 | Cosenza, 2020 | Filippetti, 2022 |
| Calvo-Lobo, 2018 | Eby, 2016 | Hara, 2018 |
| Cosenza, 2020 | Eby, 2017 | Kenis-Coskun, 2020 |
| Dias, 2017 | Gao, 2018 | Kim, 2021 |
| Fröhlich-Zwahlen, 2014 | Gao, 2018 | Moreta, 2020 |
| Hadi, 2018Hong, 2018 | Gao, 2019 | Picelli, 2012 |
| Jakubowski, 2017 | Hong, 2018 | Picelli, 2014 |
| Kesikburun, 2015 | Jakubowski, 2017 | Picelli, 2017 |
| Kim, 2021 | Kesikburun, 2015 | Picelli, 2020 |
| Lee, 2019 | Lee, 2015 | Santamato, 2014 |
| Mathevon, 2018 | Lee, 2019 | |
| Picelli, 2014 | Leng, 2019 | |
| Picelli, 2017 | Liu, 2020 | |
| Picelli. 2020 | Mathevon, 2018 | |
| Thielman, 2019 | Picelli, 2020 | |
| Yang, 2014 | Rasool, 2016 | |
| | Wu, 2017 | |
| | Yoldas, 2021 | |
| | Yasar, 2016 | |

various image artifacts. In particular, the US is subject to a locally correlated multiplicative noise called speckle, which degrades image quality and compromises diagnostic confidence.[81,82] Speckle noise is an inherent property of medical US imaging that tends to reduce the image resolution and contrast, thereby reducing the diagnostic value of this imaging modality. As a result, speckle noise reduction is essential whenever US imaging is used for tissue characterization.[83] US visual evaluation of muscle can be complex because muscles have an inhomogeneous, speckled appearance on US images. In addition, fascicles can give a strong or weak reflection, depending on size, direction, and rheological properties, making it difficult to detect slight differences in reflections. Different degrees of experience and visual judgment are also known to contribute to the relatively high rates of inter-and intra-observer variations of visual evaluation.[84]

Quantitative assessment of muscle EI is more objective and allows for statistical analysis, which is very suitable for research purposes. However, in addition to being more time-consuming, it requires normal values of each muscle EI for each US device.[85] Therefore, while one study was conducted on the reliability of the normative data between US devices,[84] this makes the quantitative analysis more difficult to apply in everyday clinical practice, particularly in an outpatient setting. In addition, system settings will strongly influence the value in both types of assessment (visual and quantitative), so it is crucial to keep all settings that can affect the yield of grey [such as the ambient light, gain, compression, focus, depth and time gain compensation (TGC), and the set frequency of the probe] constant throughout the measurements.[86]

The Heckmatt scale is commonly used for semi-quantitative assessment of EI.[84,87,88] It was originally developed by Heckmatt and Dubowitz, who proposed it as a radiologic tool to visually evaluate muscles in Duchenne muscular dystrophy.[89] One of the main advantages of semi-quantitative echogenicity assessment is that it can be performed visually by anyone with a standard US device, without the need to purchase expensive software (unlike sonoelastography).[69] There has been an increasing trend of utilization of the Heckmatt scale in patients with spasticity after stroke,[36,44,49,67-71] although it has never been explicitly validated for this population.[66] In 2020, Moreta *et al.* modified the Heckmatt scale to obtain greater specificity for the spastic muscle evaluation. Their MHS demonstrated good reliability and validity in using EI to assess pathologic muscle changes that occur in patients with spasticity.[66]

### *Utility of ultrasound assessment in clinical spasticity*

An observational study conducted by Picelli et al. explored the relationship between ultrasonographic, electromyographic, and clinical parameters in 43 stroke patients with spastic equinus.[49] They showed that spastic gastrocnemius muscle EI was directly associated with the Modified Ashworth Scale (MAS) score and inversely correlated with muscle thickness, posterior pennation angle, compound muscle action potential amplitude, and ankle passive range of motion. In the medial gastrocnemius, 37.2% were Heckmatt grade 2, 39.5% grade 3, and 23.2% grade 4. In the lateral gastrocnemius, 41.9% were Heckmatt grade 2, 39.5% grade 3, and 18.6% grade 4.[49] Since the study was conducted on patients with equinovarus, it is not surprising that the proportion of Heckmatt grade 4 was higher in the medial gastrocnemius. The authors then compared the features of spastic equinus foot in 38 patients with chronic stroke and 38 patients with multiple sclerosis.[44] They found a significant difference in muscle EI between the two groups, with a mean Heckmatt score of 3.00 in stroke patients, compared to 1.00 and 2.00 for the lateral and medial gastrocnemius respectively in patients with multiple sclerosis. Interestingly, the MAS was also higher in the stroke group.[44] Another observational study reported a mean Heckmatt score of 3.00 in the tibialis posterior of 46 stroke survivors with spastic equinovarus foot.[90]

Echogenicity has been less studied in the upper extremities, but one observational study focused on the Flexor Digitorum Superficialis (FDS) and Flexor Digitorum Profundus (FDP) muscles of 48 post-stroke patients using quantitative analysis. They showed significant differences between the cross-sectional area and EI values between affected and unaffected sites, as well as a strong correlation between mean EI (grey scale values) and Heckmatt scores. In FDS, 43.2% were Heckmatt 1 or 2, while 56.8% were Heckmatt 3 or 4. In FDP, 29.5% were Heckmatt 1 or 2, while 70.5% were Heckmatt 3 or 4.[69]

Kim *et al.* found increased EI in hemiparetic limbs compared to the normal side in stroke patients who were less than 1 month out from a first stroke.[52] The authors determined muscle EI using quantitative grey scale analysis. In addition, they measured pennation angle, fascicle length, and muscle thickness. They found reduced mean muscle thickness in the brachialis and medial gastrocnemius. However, the differences in EI between the hemiparetic and normal muscles were greater than the differences in muscle thickness, which suggests that EI is a more sensitive measure of structural change in hemiparetic muscle.[52]

US guidance is not only useful for muscle assessment, but it also has the potential to predict spasticity treatment outcomes. A prospective study by Santamato *et al.* aimed to assess the effects of Extracorporeal Shock Wave Therapy (ESWT) for the treatment of post-stroke plantar flexor muscle spasticity. They found a significant positive correlation between time since stroke onset and grade on the Heckmatt scale. In addition, they found that the reduction in spastic plantar flexor tone in response to ESWT persisted at 30 days in patients with EI graded 1, 2, and 3 on the Heckmatt scale, but not in those graded 4.[70]

Two studies specifically looked at the influence of muscle EI on the response to BoNT-A injections. The first one is a cohort study of 56 patients with spastic equinus foot resulting from stroke, followed for 4 weeks. One-third of patients had received less than 3 treatments with BoNT-A, while two-thirds had received BoNT-A at least 3 times before being enrolled in the study. Regarding their Heckmatt score, 28.6% were Heckmatt grade 2, 39.3% were grade 3, and 32.1% were grade 4. The authors observed

that patients with EI of the spastic gastrocnemius graded 2 on the Heckmatt scale showed greater improvement in spasticity than those with higher scores after injection of the same dose of BoNT-A.[68]

The second study investigating this question was a retrospective study of 102 post-stroke patients with spasticity due to lower limb paralysis, who were treated with a combination of BoNT-A injection and a 2-week inpatient multidisciplinary rehabilitation program. At baseline, 17 patients were Heckmatt grade 1, 55 were grade 2, 24 were grade 3, and 6 were grade 4. Patients were on average 63 years old, and the mean time between the onset of spasticity and BoNT-A injection was 6.3 years. They observed significant improvement in MAS scores after the combination of BoNT-A and rehabilitation. However, subjects with Heckmatt grade 4 showed less improvement in motor function compared to those whose muscle EI was classified as grades 1-3, suggesting that BoNT-A and multidisciplinary rehabilitation may not be indicated for patients with high spastic muscle EI.[67]

A publication by Filippetti *et al*. also supports the inverse correlation between response to spasticity treatment and muscle echogenicity. They observed a significant inverse association of the spastic calf muscles EI with the affected ankle dorsiflexion passive range of motion after a lidocaine diagnostic tibial nerve block, suggesting that increased EI also correlates negatively with response to treatment.[71]

A shared limitation of those three papers is that they used a non-validated tool, the original Heckmatt scale, to assess patients with spasticity. As spastic muscle may not show uniform pathologic changes throughout the entire muscle, the MHS may be a more valuable visual semi-quantitative scale that could be used in future research assessing muscle EI post-spasticity treatment.[66]

## Discussion

This narrative review of sixty-eight papers assessing the use of US in the assessment of the spastic muscle revealed four main themes: i) histological changes in the spastic muscle; ii) effects of BoNT-A on the muscle structure; iii) US modalities for muscle assessment; iv) utility of US assessment in clinical spasticity.

Histopathological studies revealed muscle atrophy as well as an increase in fatty tissue and extracellular matrix adaptation after CNS lesions in animals[23,24] and humans,[25-28] correlating with reduced range of motion and stiffness.[30,32,33] Reviews have also underlined the challenges and limitations of current methods to quantify and understand the adaptability of muscle architectural composition and stiffness.[29,30,32]

Several papers described BoNT-A injections contributing to muscle atrophy, increased collagen, and shifts in myosin-heavy chains on histological slides of animal subjects.[33] Although these changes can be translated into a decrease in muscle thickness and an increase in EI on US images, its effects on long-term functional outcomes are unknown and researchers have yet to consistently show a deleterious effect of BoNT-A injections on the treated spastic muscle with this modality.[33,36,37] Histopathological studies are less consistent in humans, and outcomes of post-BoNT-A treated muscle biopsies are less predictable.[33,35,37] There is a need for more robust research in this area.

Regarding US modalities for the assessment of spastic muscle, semi-quantitative echogenicity assessment with the Heckmatt scale has become more common.[36,44,49,67-71] It can be performed by anyone with access to a standard US device, without the need to purchase expensive software.[69] The limitation is that the Heckmatt scale has never been explicitly validated for the population with a CNS lesion,[66] unlike the MHS, which was developed to improve specificity in the spastic muscle evaluation.

In a clinical setting, US assessment of spastic muscle has multiple utilities. It is an easily accessible and useful tool to improve our understanding of the changes in muscle composition following a CNS lesion. Concerning EI specifically, studies have shown a direct correlation between muscle EI and clinical spasticity parameters like MAS, passive range of motion, and Tardieu scale.[44,49,69] It is also suggested that EI is a more sensitive measure of structural change in hemiparetic muscle compared to pennation angle, fascicle length, and muscle thickness at only one month after a stroke.[52] US guidance also has the potential to optimize spasticity treatment. Not only is there level 1 evidence that instrumented guidance (using US, electromyography, or electrical stimulation) is superior to injections done solely with manual guidance,[10] but the reduced efficacy of treatment in muscles with increased EI suggests that EI assessment should be part of our spasticity management algorithm.[67,68,70,71,73]

Our understanding of the histopathological phenomena occurring in the spastic muscle and contributing to increased passive stiffness needs to be deepened. The exact significance of increased muscle EI in human subjects with spasticity in vivo remains unclear.[32] Increased collagen, fat content, and hyaluronan,[31,91] skin changes, fascia,[21] extracellular matrix, sarcomere length, neural control, muscle atrophy, disuse,[32] muscle strength, aging, sarcopenia,[78-80,92] and genetics[29] each potentially play a role in the resulting EI, development of contractures, and response to spasticity treatment.

Despite many years of fundamental and clinical research, spasticity management remains challenging, and the outcome of our treatments is unfortunately often suboptimal. There is without a doubt a need to develop more accurate and accessible tools to assess the spastic muscle. The spasticity-validated MHS could be used in future spasticity studies involving multimodal treatment and assessment of muscle EI evolution with time. International US spasticity courses[93,94] should include an assessment of muscle and surrounding structures in their curriculum design. With the increased accessibility and affordability of the US, it will likely be an important tool in clinical spasticity practice. In addition to its key role in muscle identification and localization for chemodenervation,[10,11] US can also enhance our understanding of the consequences of CNS lesions on muscle content and may help in selecting the most appropriate treatment combination to reach our patients' goals.

In the future, large-scale multicentric prospective observational studies could be conducted to determine which factors have the most impact on muscle EI evolution and what treatment modality should be prioritized concerning the pairing of clinical and EI assessments. For example, we might opt for a more aggressive and surgical approach to manage a patient with an MAS score of 2 or more and a grade of 3 or 4 on the MHS. We can also hypothesize that by precisely delivering BoNT-A to more hypoechoic and healthy intramuscular pockets, we could optimize the outcome of our injections. Finally, US muscle assessment could aid in investigations of the pathophysiological mechanisms involved in innovative spasticity treatments such as collagenase[95] and hyaluronidase injections,[96,97] as well as cryo neurolysis,[98] and to define their place in the future algorithm of spasticity management.

## Conclusions

Animal and human studies describe muscle architectural changes after upper motor neuron injury and after BoNT-A injection. Human studies have revealed that muscle-increased EI may affect spasticity treatment outcomes. Sonoelastography and quantitative analysis of muscle EI have been shown to detect changes in muscle US architecture in spasticity, but its practical utility in clinical practice may be challenging to incorporate. The semi-quantitative validated tool MHS demonstrated good reliability and validity in assessing pathologic muscle changes in patients with spasticity and is easy to use in clinical practice. The use of US may be an important tool to assess architectural muscle changes in spasticity and improve spasticity management.

We encountered some limitations while writing this paper. As this is a narrative review, including every histologic paper on post-CNS lesion muscle changes was impossible. However, thanks to the method applied for the literature search, we are confident that we included the most relevant papers to support our main hypothesis that US is an accessible tool that could change the way we assess peripheral muscle changes in research and clinical settings. These changes remain only partially understood and require more investigation.

In the future, treatment algorithms may be developed based on the level of muscle stiffness coupled with the degree of EI to achieve patient goals. Further epidemiological studies are needed to determine the incidence of these EI changes in spastic muscles and their effect on function and treatment outcomes.

## List of abbreviations

BoNT-A: Botulinum Neurotoxin Type A,
US: Ultrasound,
EI: Echo-Intensity,
CNS: Central Nervous System,
MHS: Modified Heckmatt Scale,
TGC: Time Gain Compensation,
MAS: Modified Ashworth Scale,
FDS: Flexor Digitorum Superficialis,
FDP: Flexor Digitorum Profundus,
ESWT: Extracorporeal Shock Wave Therapy

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***Online supplementary materials***

***Table 1.*** *Characteristics of the studies included.*