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Emerging Therapies for Spastic Movement Disorder

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Abstract

Spasticity develops as a result of CNS injury; however, secondary changes within the muscles and connective tissue also contribute to muscle stiffness. The hyaluronan hypothesis postulates that the accumulation of hyaluronan, a high molecular weight glycosaminoglycan which acts as a lubricant within the extracellular matrix of muscles, promotes the development of muscle stiffness. Intramuscular injections of the enzyme hyaluronidase, which hydrolyzes long-chained hyaluronan polymers to smaller polymers, was shown to reduce muscle stiffness and increase passive and active range of motion in patients with spasticity. These results provide preliminary evidence of the hyaluronan hypothesis and suggest an emerging therapy to reduce muscle stiffness using the enzyme hyaluronidase.

Keywords

Spasticity; Muscle stiffness; Peripheral mechanism; Stroke; Brain Injury; Hyaluronidase; Hyaluronic Acid; Hyaluronan hypothesis

Introduction

Muscle stiffness and spasticity cause severe disability in approximately 12 million people after neurologic injury of cerebral or spinal origin, such as stroke, cerebral palsy, spinal cord injury, and multiple sclerosis [1]. The prevalence of spasticity increases over weeks and months after the neurologic injury [2], leading to muscle stiffness which persists for years, contributing to further disability, and slowed recovery. Upper limb spasticity, and muscle stiffness are associated with reduced functional independence and a four-fold increase in direct care costs during the first year post-stroke alone [3 4]. They are challenging to treat because the underlying mechanisms are not fully understood [4 5].

Spasticity is classically defined as a velocity-dependent increase in tonic stretch reflexes resulting from hyper-excitability of the stretch reflex [6] because of decreased cortical

Disclosures

New York University has filed a patent on the Use of Hyaluronidase for Muscle Stiffness. Dr. Raghavan is co-founder of MovEase, Inc. This article discusses the off-label use of hyaluronidase for muscle stiffness.

influences on the inhibitory brainstem descending pathways to the spinal cord [7]. The imbalance between inhibitory cortical and brainstem pathways from the ventromedial reticular formation and the excitatory brainstem pathways from the bulbopontine tegmentum and the vestibular nucleus are thought to reduce pre-synaptic inhibition causing spasticity [8] **(Figure 1)**. However, hyperreflexia is only one component of the problem in patients with spasticity [9–11], and the extent of hyperrelflexia may not be correlated with the extent of muscle stiffness [12 13]. Nevertheless, CNS depressants (e.g., benzodiazepines, baclofen, and tizanidine) are commonly used to treat "hyperactivity," but they also produce muscle weakness, fatigue, and sleepiness [14]. Botulinum toxin injections are effective in reducing "muscle over-activity" in patients with spasticity, but it has long been known that muscles can be stiff even in the absence of EMG activation [15]. Thus, while neural mechanisms certainly initiate spasticity, non-neural peripheral mechanisms clearly play a role in the development and exacerbation of muscle stiffness [16 17].

Increased resistance to passive stretch can occur because of secondary non-neural changes in muscle fibers, collagen tissue, and tendon properties [18 19]. Early experiments on muscle properties [20] showed that the faster the change in muscle length, the greater is the passive tension generated in the muscle in the absence of muscle activation. This can be quantified with the length-tension curve, which shows a steeper slope in spastic compared with non-spastic muscles at equivalent speeds **(Figure 2)**. This non-neural, or passive stiffness, is distinct from the increase in EMG activity (neural response) when a muscle is stretched at faster speeds [21] and can lead to the generation of increased torques despite the presence of weakness [22 23]. A previous hypothesis postulated that passive muscle stiffness may increase because of sarcomere shortening resulting from intracellular changes in the configuration of titin, the major passive load-bearing protein within the muscle fiber. However, subsequent studies found that the sarcomere is *lengthened* in patients with contracture [24 25]. Also, the titin isoform and passive mechanics of individual muscle fibers are unaltered in spastic muscles, although muscle fascicles are stiffer [26], suggesting that passive stiffness may arise from alterations in the extracellular matrix (ECM).

The thickness of the ECM is increased in chronically spastic muscles, particularly the endomysium, perimysium, and epimysium that are made up of collagen (types I and III) [27] **(Figure 3)**. Therefore, fibrosis and contracture were thought to produce muscle stiffness. If so, one would expect spastic muscle bundles to generate higher tension relative to normal muscle bundles. Surprisingly, spastic muscle bundles showed significantly lower tension (tangent modulus) than non-spastic muscle bundles [28]. Recent studies do not support a role for increased content and disorganization of collagen in muscle stiffness, although they have been the prime contenders for the development of passive muscle stiffness [29 30]. Thus, the precise non-neural mechanisms of muscle stiffness are still not fully understood.

An alternative explanation: the hyaluronan hypothesis.

We proposed that hyaluronan, a non-sulfated high molecular weight glycosaminoglycan (GAG), and a major component of the ECM surrounding the endomysium, perimysium, and epimysium [31], which normally provides lubrication to facilitate sliding and myofascial force transmission within and between muscles [32], could potentially contribute to muscle

stiffness after cerebral injury. This hypothesis was based on three main findings. First, muscle fiber atrophy after upper motor neuron injury in the context of paresis, leads to a relative increase in the proportion of the ECM [33 34], which could be occupied by hyaluronan [35]. Second, immobilization of the ankle joint in rats led to increased hyaluronan accumulation in the soleus muscle after four weeks (**Figure 4**), around the endomysium and perimysium, which was hydrolyzed with Streptomyces hyaluronidase [36]. After 12 weeks the endomysium also thickened **(Figure 5)**. Third, at high concentrations, hyaluronan and protein-crosslinked assemblies of hyaluronan, aggregate [37] and dramatically increase the viscoelasticity of the ECM [38]. These large aggregated molecules cannot be cleared particularly when mobility is reduced. Thus, hyper-viscous hyaluronan in the ECM can cause the muscle fibers and fascicles to stick to one another, reduce gliding during movement, and increase muscle stiffness **(Figure 6)**.

Preliminary evidence for the hyaluronan hypothesis and an emerging treatment

Human recombinant hyaluronidase (Hylenex, Halozyme Therapeutics, Inc.) is commercially available, safe in children and adults, and FDA-approved since 2005 for use as a tissue permeability modifier. It is currently indicated as an adjuvant in subcutaneous fluid administration for achieving hydration, to increase the dispersion and absorption of other injected drugs, and in subcutaneous urography for improving resorption of radiopaque agents.

In our recent retrospective case series [39], twenty patients with unilateral upper limb spasticity of cerebral origin received off-label injections of human recombinant hyaluronidase in combination with preservative-free normal saline into 6–8 upper-limb muscles at a single visit. All patients (mean age 41±22 years and mean time since injury 40.6±38.9 months) had moderately severe-unilateral upper-limb spasticity in more than one joint, defined by Modified Ashworth Scale (MAS) score >2. The dose ranged from 450–600 units of hyaluronidase (3–4 vials of 150 units/mL) diluted with normal saline in a 1:1 ratio and given in multiple synergistically acting muscles **(Figure 7)**.

There were no clinically significant adverse effects related to the treatment. Patients' passive and active range of motion was evaluated pre- and post-injection to assess clinical response to treatment. Passive movement at all joints, and active movement at most joints increased within 2 weeks post-injection (T1), and persisted at 4–6 weeks post-injection (T2), and 3–5 months post-injection (T3) for most joints **(Figure 8)**. There was a delayed increase in active elbow extension and forearm pronation, suggesting a possible interaction with neural mechanisms and motor learning. The percentage of joints with MAS=3 decreased by 38.5%, and those with MAS=0 increased by 46.9% within 3 days to 2 weeks, suggesting that this was a clear effect of the injections **(Figure 9)**. The results persisted for at least 3 months. Most importantly there were no side effects of muscle weakness or sedation. These results provide preliminary evidence that intramuscular hyaluronidase injection can reduce muscle stiffness and increase passive and active movement in multiple upper-limb joints of patients with chronic spasticity.

Summary

Although spasticity develops as a result of neural mechanisms, muscle stiffness in spastic patients may occur as a result of peripheral non-neural mechanisms. The hyaluronan hypothesis postulates that the accumulation of hyaluronan within the ECM of muscle may lead to muscle stiffness. In a retrospective case series we found that injections of hyaluronidase into upper-limb muscles not only decreased muscle stiffness and increased passive movement but also increased active movement [39], providing preliminary evidence for the hyaluronan hypothesis. Increased levels of hyaluronan have also been shown to precede fibrosis in several organs [40–44]; therefore, hydrolysis of hyaluronan by hyaluronidase in muscle may potentially stop the progression to fibrosis, contracture, and disability. Confirmation of the findings and elucidation of the underlying mechanisms will result in a new treatment for a major disabling problem. A better understanding of the mechanisms underlying muscle stiffness, and the basis for treatment with hyaluronidase, can potentially transform clinical practice for the treatment of muscle stiffness after neurological injury. Other treatments may also target this mechanism and future studies may lead to elucidation of these treatments.

Acknowledgements

Thanks to Dr. Susie Kwon for the drawing representing the hyaluronan hypothesis and treatment with hyaluronidase.

References

1. Sommerfeld DK, Eek EU, Svensson AK, Holmqvist LW, von Arbin MH. Spasticity after stroke: its occurrence and association with motor impairments and activity limitations. Stroke 2004;35(1):134–9 doi: 10.1161/01.STR.0000105386.05173.5E01.STR.0000105386.05173.5E[pii][published Online First: Epub Date]. [PubMed: 14684785]
2. Watkins CL, Leathley MJ, Gregson JM, Moore AP, Smith TL, Sharma AK. Prevalence of spasticity post stroke. Clin Rehabil 2002;16(5):515–22 [PubMed: 12194622]
3. Lundstrom E, Smits A, Borg J, Terent A. Four-fold increase in direct costs of stroke survivors with spasticity compared with stroke survivors without spasticity: the first year after the event. Stroke 2010;41(2):319–24 doi: 10.1161/STROKEAHA.109.558619STROKEAHA.109.558619[pii] [published Online First: Epub Date]|. [PubMed: 20044535]
4. Zorowitz RD, Gillard PJ, Brainin M. Poststroke spasticity: sequelae and burden on stroke survivors and caregivers. Neurology 2013;80(3 Suppl 2):S45–52 doi: 10.1212/WNL.0b013e3182764c8680/3_Supplement_2/S45[pii][published Online First: Epub Date]|.
5. Francisco GE, McGuire JR. Poststroke spasticity management. Stroke 2012;43(11):3132–6 doi: 10.1161/STROKEAHA.111.639831STROKEAHA.111.639831 [pii][published Online First: Epub Date]|. [PubMed: 22984012]
6. Lance JW. The control of muscle tone, reflexes, and movement: Robert Wartenberg Lecture. Neurology 1980;30(12):1303–13 [PubMed: 7192811]
7. Sheean G, McGuire JR. Spastic hypertonia and movement disorders: pathophysiology, clinical presentation, and quantification. PM R 2009;1(9):827–33 doi: 10.1016/j.pmrj.2009.08.002S1934-1482(09)00763-1 [pii] [published Online First: Epub Date]|. [PubMed: 19769916]
8. Sheean G The pathophysiology of spasticity. Eur J Neurol 2002;9 Suppl 1:3–9; dicussion 53–61 doi: 058[pii][published Online First: Epub Date]|. [PubMed: 11918643]

9. Sinkjaer T, Toft E, Larsen K, Andreassen S, Hansen HJ. Non-reflex and reflex mediated ankle joint stiffness in multiple sclerosis patients with spasticity. Muscle Nerve 1993;16(1):69–76 doi: 10.1002/mus.880160112[published Online First: Epub Date]|. [PubMed: 8423835]
10. Schindler-Ivens SM, Shields RK. Soleus H-reflex recruitment is not altered in persons with chronic spinal cord injury. Arch Phys Med Rehabil 2004;85(5):840–7 doi: S0003999303010633[pii] [published Online First: Epub Date]|. [PubMed: 15129411]
11. Wilson LR, Gracies JM, Burke D, Gandevia SC. Evidence for fusimotor drive in stroke patients based on muscle spindle thixotropy. Neurosci Lett 1999;264(1– 3):109–12 [PubMed: 10320026]
12. O'Dwyer NJ, Ada L. Reflex hyperexcitability and muscle contracture in relation to spastic hypertonia. Curr Opin Neurol 1996;9(6):451–5 [PubMed: 9007404]
13. O'Dwyer NJ, Ada L, Neilson PD. Spasticity and muscle contracture following stroke. Brain 1996; 119 (Pt 5):1737–49 [PubMed: 8931594]
14. McIntyre A, Lee T, Janzen S, Mays R, Mehta S, Teasell R. Systematic review of the effectiveness of pharmacological interventions in the treatment of spasticity of the hemiparetic lower extremity more than six months post stroke. Top Stroke Rehabil 2012;19(6):479–90 doi: 10.1310/tsr1906-479R543441H71757078 [pii][published Online First: Epub Date]|. [PubMed: 23192713]
15. Gracies JM, Brashear A, Jech R, et al. Safety and efficacy of abobotulinumtoxinA for hemiparesis in adults with upper limb spasticity after stroke or traumatic brain injury: a double-blind randomised controlled trial. Lancet Neurol 2015;14(10):992–1001 doi: 10.1016/S1474-4422(15)00216-1S1474-4422(15)00216-1 [pii][published Online First: Epub Date]|. [PubMed: 26318836]
16. Burke D, Wissel J, Donnan GA. Pathophysiology of spasticity in stroke. Neurology 2013;80(3 Suppl 2):S20–6 doi: 10.1212/WNL.0b013e31827624a780/3_Supplement_2/S20 [pii][published Online First: Epub Date]|.
17. Stecco A, Stecco C, Raghavan P. Peripheral mechanisms of spasticity and treatment implications. Current Physical Medicine and Rehabilitation Reports 2014 doi: 10.1007/s40141-014-0052-3[published Online First: Epub Date]|.
18. Foran JR, Steinman S, Barash I, Chambers HG, Lieber RL. Structural and mechanical alterations in spastic skeletal muscle. Dev Med Child Neurol 2005;47(10):713–7 doi: S0012162205001465 [pii] 10.1017/S0012162205001465[published Online First: Epub Date]|. [PubMed: 16174321]
19. Dietz V, Sinkjaer T. Spastic movement disorder: impaired reflex function and altered muscle mechanics. Lancet Neurol 2007;6(8):725–33 doi: S1474-4422(07)70193-X[pii]10.1016/S1474-4422(07)70193-X[published Online First: Epub Date]|. [PubMed: 17638613]
20. Hill AV. First and last experiments in muscle mechanics Cambridge: Cambridge University Press, 1970.
21. Ibrahim IK, Berger W, Trippel M, Dietz V. Stretch-induced electromyographic activity and torque in spastic elbow muscles. Differential modulation of reflex activity in passive and active motor tasks. Brain 1993;116 (Pt 4):971–89 [PubMed: 8353719]
22. Hufschmidt A, Mauritz KH. Chronic transformation of muscle in spasticity: a peripheral contribution to increased tone. J Neurol Neurosurg Psychiatry 1985;48(7):676–85 [PubMed: 4031912]
23. Schmit BD, Dhaher Y, Dewald JP, Rymer WZ. Reflex torque response to movement of the spastic elbow: theoretical analyses and implications for quantification of spasticity. Ann Biomed Eng 1999;27(6):815–29 [PubMed: 10625153]
24. Lieber RL, Ponten E, Burkholder TJ, Friden J. Sarcomere length changes after flexor carpi ulnaris to extensor digitorum communis tendon transfer. J Hand Surg Am 1996;21(4):612–8 doi: S0363-5023(96)80012-8[pii] 10.1016/S0363-5023(96)80012-8[published Online First: Epub Date]|. [PubMed: 8842952]
25. Lieber RL, Friden J. Intraoperative measurement and biomechanical modeling of the flexor carpi ulnaris-to-extensor carpi radialis longus tendon transfer. J Biomech Eng 1997;119(4):386–91 [PubMed: 9407275]
26. Smith LR, Lee KS, Ward SR, Chambers HG, Lieber RL. Hamstring contractures in children with spastic cerebral palsy result from a stiffer extracellular matrix and increased in vivo sarcomere

length. J Physiol 2011;589(Pt 10):2625–39 doi: 10.1113/jphysiol.2010.203364jphysiol.2010.203364 [pii][published Online First: Epub Date]|. [PubMed: 21486759]

27. de Bruin M, Smeulders MJ, Kreulen M, Huijing PA, Jaspers RT. Intramuscular connective tissue differences in spastic and control muscle: a mechanical and histological study. PLoS One 2014;9(6):e101038 doi: 10.1371/journal.pone.0101038PONE-D-13-53999 [pii][published Online First: Epub Date]|. [PubMed: 24977410]
28. Lieber RL, Runesson E, Einarsson F, Friden J. Inferior mechanical properties of spastic muscle bundles due to hypertrophic but compromised extracellular matrix material. Muscle Nerve 2003;28(4):464–71 doi: 10.1002/mus.10446[published Online First: Epub Date]|. [PubMed: 14506719]
29. Chapman MA, Pichika R, Lieber RL. Collagen crosslinking does not dictate stiffness in a transgenic mouse model of skeletal muscle fibrosis. J Biomech 2015;48(2):375–8 doi: 10.1016/j.jbiomech.2014.12.005S0021-9290(14)00659-9 [pii][published Online First: Epub Date]|. [PubMed: 25529136]
30. Smith LR, Barton ER. Collagen content does not alter the passive mechanical properties of fibrotic skeletal muscle in mdx mice. Am J Physiol Cell Physiol 2014;306(10):C889–98 doi: 10.1152/ajpcell.00383.2013ajpcell.00383.2013 [pii][published Online First: Epub Date]|. [PubMed: 24598364]
31. Piehl-Aulin K, Laurent C, Engstrom-Laurent A, Hellstrom S, Henriksson J. Hyaluronan in human skeletal muscle of lower extremity: concentration, distribution, and effect of exercise. J Appl Physiol (1985) 1991;71(6):2493–8 [PubMed: 1778950]
32. Purslow PP, Trotter JA. The morphology and mechanical properties of endomysium in series-fibred muscles: variations with muscle length. J Muscle Res Cell Motil 1994; 15(3):299–308 [PubMed: 7929795]
33. Dietz V, Berger W. Cerebral palsy and muscle transformation. Dev Med Child Neurol 1995;37(2):180–4 [PubMed: 7851674]
34. Springer J, Schust S, Peske K, et al. Catabolic signaling and muscle wasting after acute ischemic stroke in mice: indication for a stroke-specific sarcopenia. Stroke 2014;45(12):3675–83 doi: 10.1161/STROKEAHA.114.006258STROKEAHA.114.006258 [pii][published Online First: Epub Date]|. [PubMed: 25352483]
35. Girish KS, Kemparaju K. The magic glue hyaluronan and its eraser hyaluronidase: a biological overview. Life Sci 2007;80(21):1921–43 doi: S0024–3205(07)00210-X[pii] 10.1016/j.lfs.2007.02.037[published Online First: Epub Date]|. [PubMed: 17408700]
36. Okita M, Yoshimura T, Nakano J, Motomura M, Eguchi K. Effects of reduced joint mobility on sarcomere length, collagen fibril arrangement in the endomysium, and hyaluronan in rat soleus muscle. J Muscle Res Cell Motil 2004;25(2):159–66 [PubMed: 15360131]
37. Zhao M, Yoneda M, Ohashi Y, et al. Evidence for the covalent binding of SHAP, heavy chains of inter-alpha-trypsin inhibitor, to hyaluronan. J Biol Chem 1995;270(44):26657–63 [PubMed: 7592891]
38. Cowman MK, Schmidt TA, Raghavan P, Stecco A. Viscoelastic Properties of Hyaluronan in Physiological Conditions. F1000Res 2015;4:622 doi: 10.12688/f1000research.6885.1[published Online First: Epub Date]|. [PubMed: 26594344]
39. Raghavan P, Lu Y, Mirchandani M, Stecco A. Human Recombinant Hyaluronidase Injections For Upper Limb Muscle Stiffness in Individuals With Cerebral Injury: A Case Series. EBioMedicine 2016;9:306–13 doi: 10.1016/j.ebiom.2016.05.014S2352-3964(16)30197-9 [pii][published Online First: Epub Date]|. [PubMed: 27333050]
40. Bensadoun ES, Burke AK, Hogg JC, Roberts CR. Proteoglycan deposition in pulmonary fibrosis. Am J Respir Crit Care Med 1996;154(6 Pt 1):1819–28 doi: 10.1164/ajrccm.154.6.8970376[published Online First: Epub Date]|. [PubMed: 8970376]
41. Evanko SP, Potter-Perigo S, Petty LJ, Workman GA, Wight TN. Hyaluronan Controls the Deposition of Fibronectin and Collagen and Modulates TGF-beta1 Induction of Lung Myofibroblasts. Matrix Biol 2015;42:74–92 doi: 10.1016/j.matbio.2014.12.001S0945-053X(14)00222-4 [pii][published Online First: Epub Date]|. [PubMed: 25549589]

42. Jun Z, Hill PA, Lan HY, et al. CD44 and hyaluronan expression in the development of experimental crescentic glomerulonephritis. Clin Exp Immunol 1997;108(1):69–77 [PubMed: 9097914]

43. Hernnas J, Nettelbladt O, Bjermer L, Sarnstrand B, Malmstrom A, Hallgren R. Alveolar accumulation of fibronectin and hyaluronan precedes bleomycin-induced pulmonary fibrosis in the rat. Eur Respir J 1992;5(4):404–10 [PubMed: 1373389]

44. Halfon P, Bourliere M, Penaranda G, et al. Accuracy of hyaluronic acid level for predicting liver fibrosis stages in patients with hepatitis C virus. Comp Hepatol 2005;4:6 doi: 1476-5926-4-6[pii] 10.1186/1476-5926-4-6[published Online First: Epub Date]|. [PubMed: 16008833]

Key Points:

- Neural mechanisms of spasticity do not fully explain the motor dysfunction in patients with spastic disorders.
- Peripheral non-neural mechanisms are not fully understood.
- The hyaluronan hypothesis postulates that the accumulation of hyaluronan, which functions as a lubricant in the extracellular matrix of muscle, may lead to the development of muscle stiffness.
- Hydrolysis of the accumulated hyaluronan may be safely achieved using local injections of the enzyme hyaluronidase to reduce muscle stiffness and increase both passive and active motion.
- Hyaluronidase is a potential emerging treatment for the management of patients with spastic movement disorder.

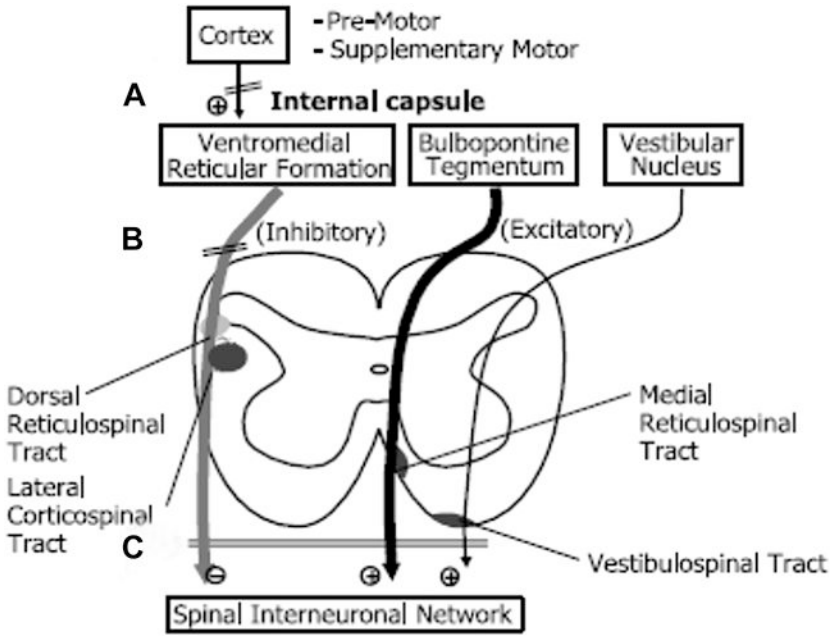

Figure 1.

Central nervous system injury disrupts inhibitory descending pathways controlling spinal stretch reflex excitability. A = Corticobulbar fibers; B = Dorsal reticulospinal pathway; C = Loss of all supraspinal control.

From Sheean G. The pathophysiology of spasticity. Eur J Neurol 2002; 9 (Suppl. 1); 3–9; with permission.

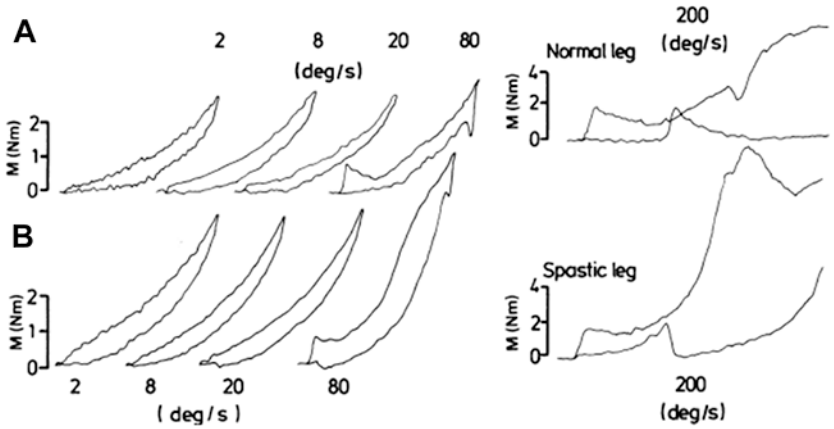

Figure 2.

Increased slope of the passive length-tension curve at faster speeds in spastic muscles (b) compared to non-spastic muscles on the unaffected side (a).

From Hufschmidt A, Mauritz KH. Chronic transformation of muscle in spasticity: a peripheral contribution to increased tone. J Neurol Neurosurg Psychiatry 1985; 48;7;676–685; with permission.

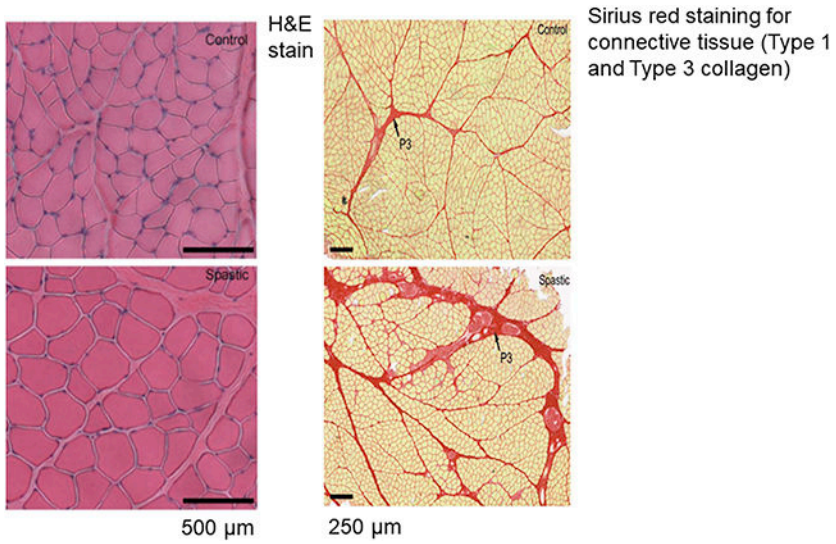

Figure 3.

Chronically spastic muscles show increased endomysial and perimysial thickness that stain for Type 1 and Type 3 collagen suggesting fibrosis.

From de Bruin M, Smeulders MJ, Kreulen M, et al. Intramuscular connective tissue differences in spastic and control muscle: a mechanical and histological study. PLoS One 2014;9;6; e101038; with permission.

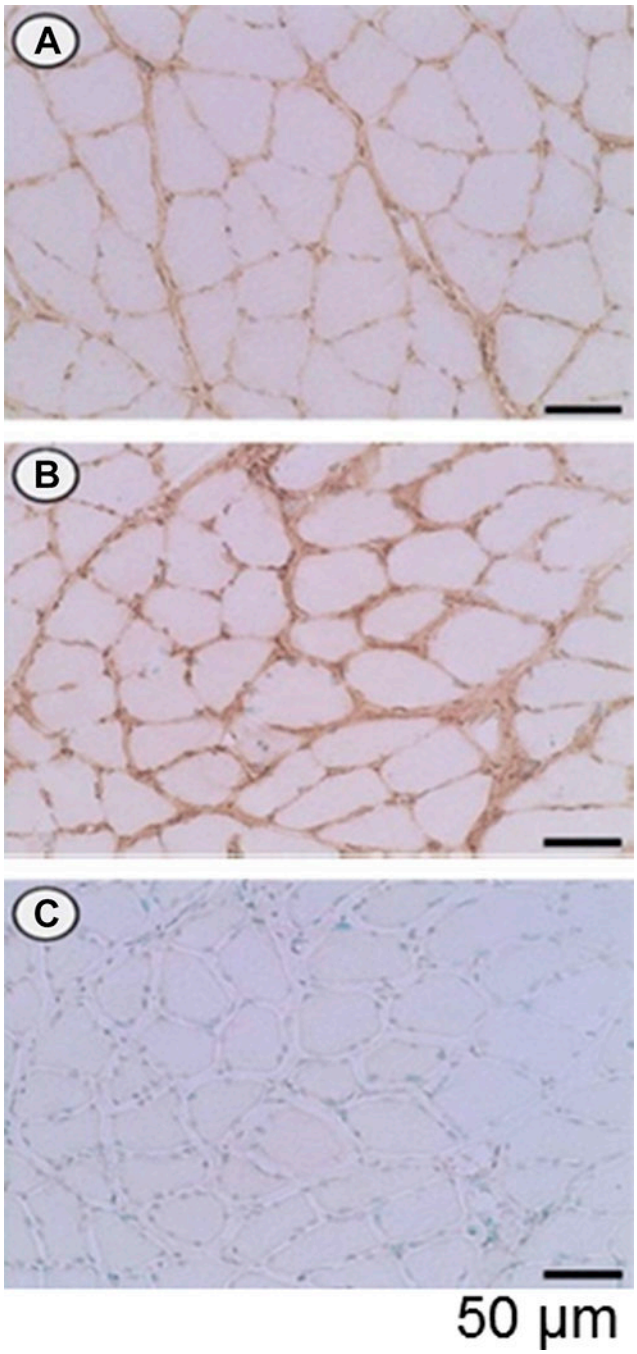

Figure 4.

Sections of soleus muscle in 12-week-old rats showing accumulation of hyaluronan (stained brown with Hyaluronic Acid binding protein) compared with control animals (A) after 4-weeks of immobilization (B), which was hydrolyzed after treatment with Streptomyces Hyaluronidase (C).

From Okita M, Yoshimura T, Nakano J, et al. Effects of reduced joint mobility on sarcomere length, collagen fibril arrangement in the endomysium, and hyaluronan in rat soleus muscle. J Muscle Res Cell Motil; 2004;25;2;159–66; with permission.

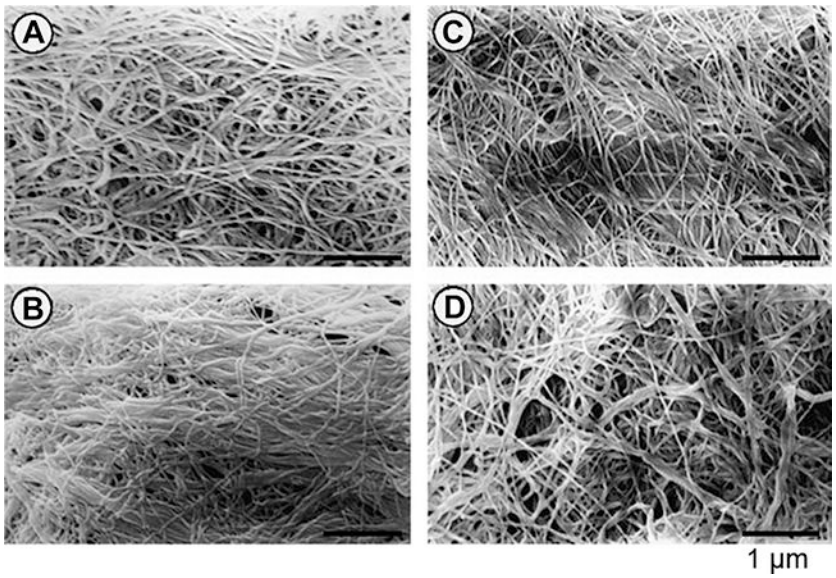

Figure 5.

Scanning electron micrographs showing gradual thickening of soleus muscle endomysia compared with control animals (A) after 2 weeks of immobilization (B), after 4 weeks of immobilization (C) and particularly after 12 weeks of immobilization (D).

From Okita M, Yoshimura T, Nakano J, et al. Effects of reduced joint mobility on sarcomere length, collagen fibril arrangement in the endomysium, and hyaluronan in rat soleus muscle. J Muscle Res Cell Motil; 2004;25;2;159–66; with permission.

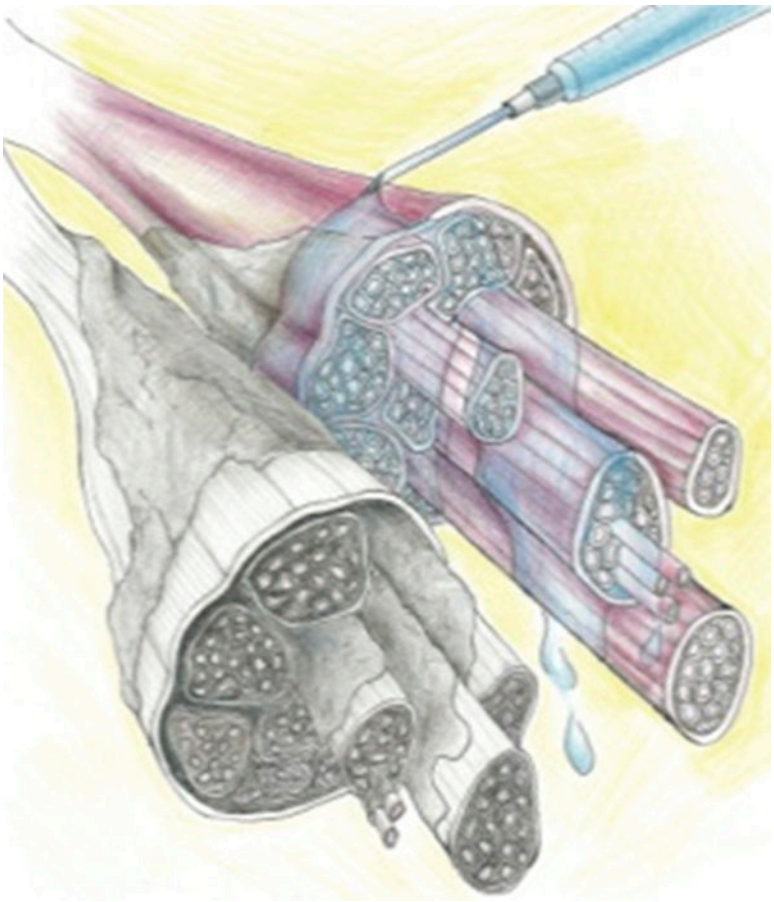

Figure 6.

The hyaluronan hypothesis. The dark patches represent aggregates of hyaluronan. Injection of the enzyme hyaluronidase can potentially hydrolyze the hyaluronan deposits, and restore sliding of the muscle fibers and fascicles.

Courtesy of Dr. Susie Kwon, MD, NY, New York.

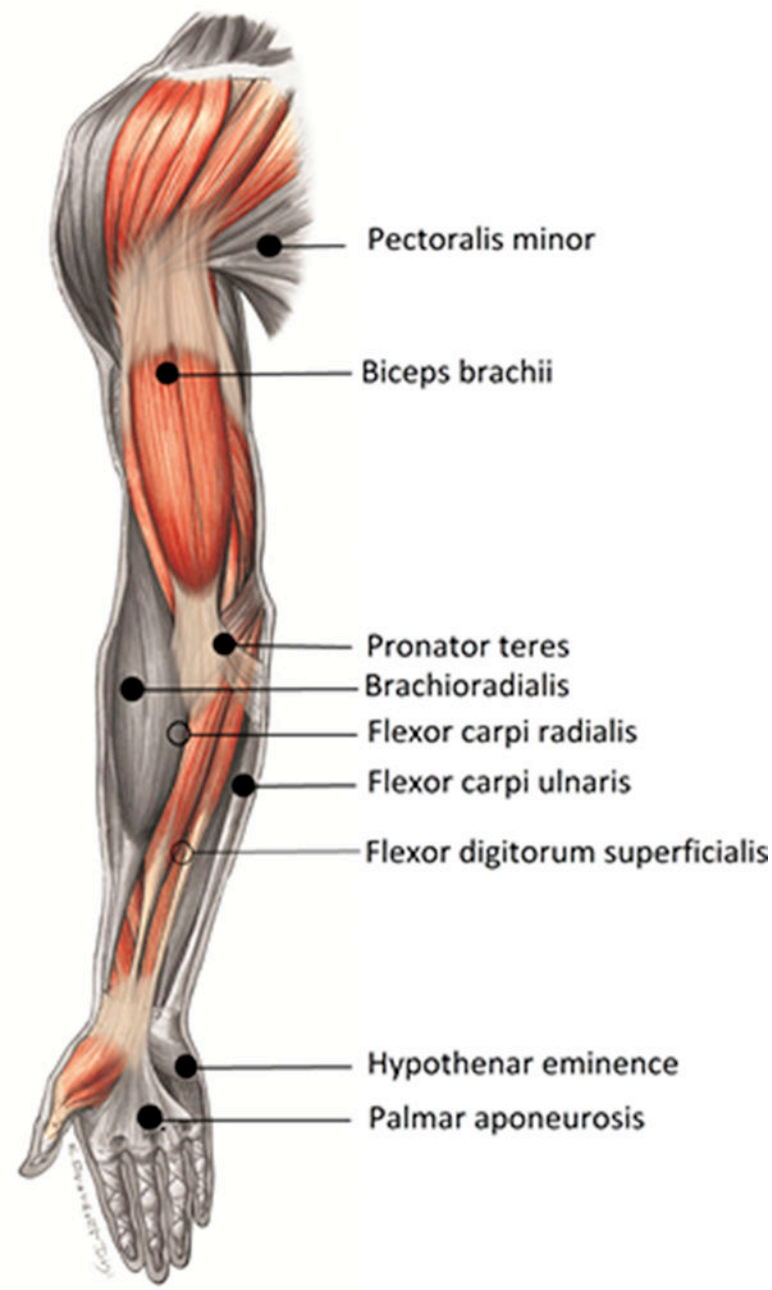

Figure 7.

Common sites of injection with hyaluronidase.

From Raghavan P, Lu Y, Mirchandani M, et al. Human Recombinant Hyaluronidase Injections for Upper Limb Muscle Stiffness in Individuals with Cerebral Injury: A Case Series. EBioMedicine; 2016;9;306–313; with permission.

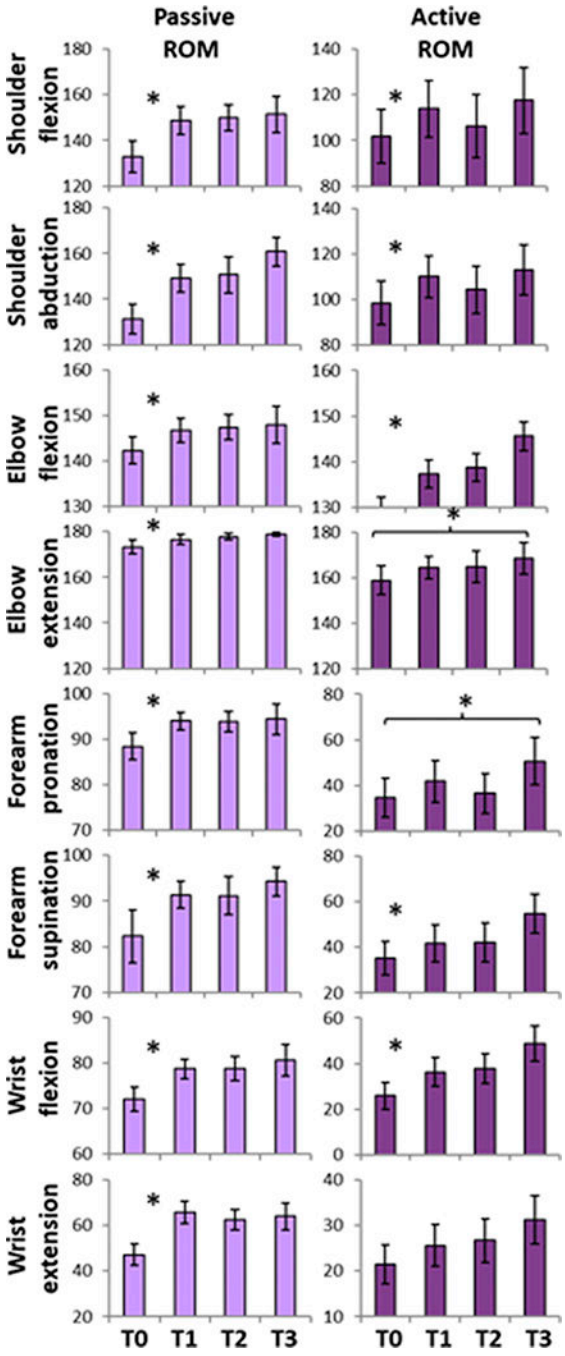

Figure 8.

Active and passive range of motion at T0= pre-injection, T1= within 2 weeks post-injection, T2= within 4–6 weeks post-injection, and T3= within 3–5 months post-injection.

Data from Raghavan P, Lu Y, Mirchandani M, et al. Human Recombinant Hyaluronidase Injections for Upper Limb Muscle Stiffness in Individuals with Cerebral Injury: A Case Series. EBioMedicine; 2016;9;306–313; with permission.

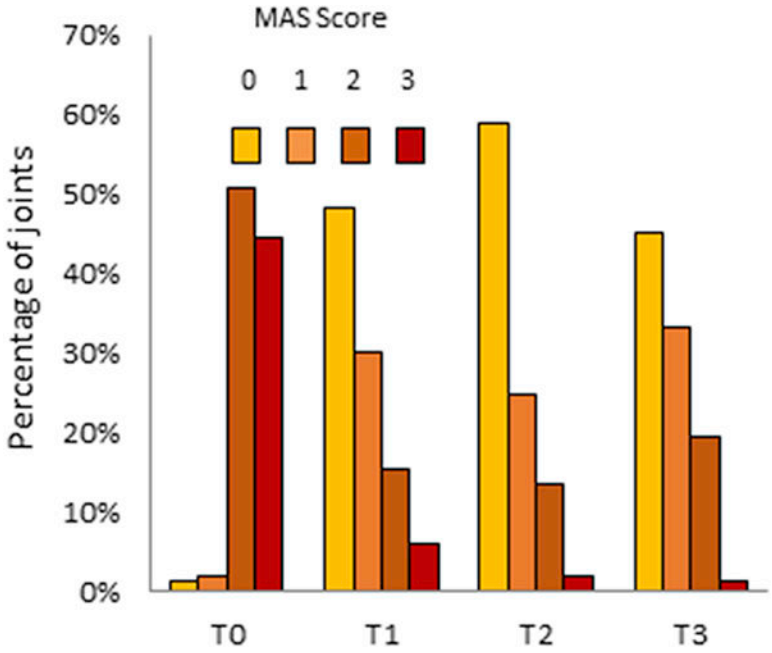

Figure 9.

MAS score across all the upper limb joints.

Data from Raghavan P, Lu Y, Mirchandani M, et al. Human Recombinant Hyaluronidase Injections for Upper Limb Muscle Stiffness in Individuals With Cerebral Injury: A Case Series. EBioMedicine; 2016;9;306–313; with permission.