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Conference Report on Contractures in Musculoskeletal and Neurological Conditions

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This article summarizes the research findings presented and topics discussed at the meeting. The views expressed in this article are the opinions of the authors and are not intended to represent of the viewpoint of the National Institutes of Health or its Institutes.

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Abstract

Limb contractures are debilitating complications associated with various muscle and nervous system disorders. This report summarizes a conference at the Shirley Ryan AbilityLab in Chicago, IL on April 19–20, 2018 involving researchers and physicians from diverse disciplines convened to discuss current clinical and preclinical understanding of contractures in Duchenne muscular dystrophy, stroke, cerebral palsy and other conditions. Presenters described changes in muscle architecture, activation, extracellular matrix, satellite cells and muscle fiber sarcomeric structure that accompany or predispose muscles to contracture. Participants identified ongoing and future research directions that may lead to understanding of the intersecting factors that trigger contractures. These include additional studies of changes in muscle, tendon, joint and neuronal tissues during contracture development using imaging, molecular and physiologic approaches. Participants identified the need for improved biomarkers and outcome measures to identify patients likely to develop contractures and to accurately measure efficacy of treatments currently available and under development.

Keywords

Contracture; Duchenne muscular dystrophy; stroke; cerebral palsy; muscle

Purpose of the workshop

A research conference was held at the Shirley Ryan AbilityLab in Chicago, IL on April 19–20, 2018 to discuss the causes and treatments of contractures, debilitating consequences of a wide range of conditions including primary myopathies such as Duchenne muscular dystrophy (DMD) and neurological conditions that affect muscle such as stroke and cerebral palsy (CP). Presenters from the meeting are authors of this article. The goals of the meeting were to promote discussion and collaborations among researchers with diverse expertise, gain insights into the causes of contractures, assess biomarkers and current treatments, and identify gaps in understanding that, if addressed, could lead to more effective evidence-based treatments.

Contractures and Patient impact

There is no universally accepted definition of limb contracture, but reduced range of motion (ROM), accompanied by increased mechanical resistance at the ends of the available range are accepted clinical signs. Contractures in neuromuscular conditions are associated with reduced muscle belly length while tendon length is less affected.[1–3] Among the neurological and musculoskeletal conditions associated with contracture, the effects on muscle vary. Some conditions cause muscle hyperactivity, while others cause paralysis or degeneration of muscle fibers and replacement by non-contractile tissue. Muscle weakness or hyperactivity can increase joint static positioning, which may trigger contractures if other predisposing factors are present. Joint pain can be a predictor and/or consequence of contractures in some patients.[4,5] Contractures cause significant burden on patients due to altered body positioning, decreased independence in performing activities of daily living, and reduced community participation contributing to social isolation and decreased quality of life.

Contractures in Duchenne Muscular Dystrophy

Muscular dystrophies are associated with muscle weakness and the replacement of muscle by fat and fibrotic tissue, which contributes to contractures in some patients.[2] Researchers studying the natural history of DMD discussed data on the patterns of contracture involvement and progression. Altered gait biomechanics resulting from weakness in knee and hip extensors increases the risk that individuals develop ankle equinus contracture prior to loss of ambulation, but wheelchair reliance is most frequently due to muscle weakness rather than contractures.[6] In non-ambulant individuals, when static positioning is more prevalent and weakness does not allow full movement against gravity, contractures develop in the hips and knees.[6–8,] Subsequent upper extremity weakness leads to static positioning and contractures in the elbows and wrists. The inability of muscles to move a joint through the full ROM predisposes the joint to contracture.[2] Imbalance in the strength of opposing agonist and antagonist muscles may contribute to this inability in some conditions, although in DMD there is not an association between muscle strength imbalance around a joint and contracture frequency or severity.[6] Contracture progression in DMD is further complicated by muscle fiber degeneration and tissue fibrosis.[2] Mouse models of muscular dystrophies exhibit progressive muscle weakness and some exhibit muscle fibrosis, but dystrophic mice do not develop obvious contractures. Presenters described considerable variability in contracture formation in people living with DMD. For example, 50% of participants in an ongoing study of magnetic resonance imaging (MRI) biomarkers developed knee contractures >20 degrees soon after loss of ambulation, however 20% of participants maintained full ROM. (Willcocks, unpublished data). Additional studies are needed to identify genetic and/or environmental factors that allow some patients to avoid contractures.

Contractures in Neurological Conditions

Contractures are associated with upper motor neuron (UMN) disorders (e.g., CP, stroke) and lower motor neuron (LMN) disorders (e.g., Charcot Marie Tooth disease). Weakness is common in UMN and LMN disorders. The limb muscles of patients with UMN disorders often exhibit spasticity; the velocity-dependent increase in tonic stretch reflexes that can lead to muscle over-activation or coactivation of antagonistic muscles resulting in muscle stiffness. However, spasticity is neither sufficient nor required for contractures to develop.[9]

Cellular and extracellular matrix (ECM) changes in muscle associated with contractures were discussed. Studies of tissue obtained from CP patients demonstrate that the population of muscle-regenerating satellite cells is decreased by 60–70% in contracted muscle.[10]

Furthermore, the capacity of the remaining satellite cells to generate muscle cells is diminished, owing to epigenetic changes that affect expression of myogenic genes.[11] The ECM sheaths that separate muscle fibers exhibit increased collagen accumulation in contracted muscle, contributing to tissue stiffness.[12]

Presenters also discussed the ability of healthy muscle to adjust the number of sarcomeres per myofibril to optimize filament overlap for force production, achieving a proper sarcomere “setpoint.” In individuals with CP, sarcomere setpoint regulation appears disrupted, since muscle fascicle lengths can be normal, while the number of sarcomeres is significantly reduced. Sarcomeres at longer than optimal lengths may contribute to contracture pathogenesis.[13] This disrupted sarcomere setpoint phenomenon has not been observed in mice or non-human primates. Further research is needed to understand mechanisms that regulate sarcomere number and to determine whether disruption of this regulation is common to conditions other than CP.

Measurement of Contractures and Biomarkers

Participants at the meeting presented data on the measurement of musculoskeletal anatomy, joint ROM, musculoskeletal tissue architecture, composition and biomechanics in relation to contractures. The goniometer is the primary instrument to measure the joint angles that determine ROM and contracture severity. Video-based motion analysis is also used to measure ROM. Other clinical devices used to measure muscle biomechanical properties were discussed including the myotonometer to measure muscle tone for individuals with UMN signs.[14] Ultrasound can measure tendon and muscle kinematics, in particular fascicle length and pennation angle in real-time during static and dynamic tasks. Ultrasound shear wave elastography provides an indirect estimate of tissue stiffness in localized muscle regions.[15]. Electrical impedance myography (EIM), which assesses the muscle-induced alteration in a surface-applied current, is sensitive to myofiber cross-sectional area.[16] It thus has the potential to measure myofiber deformability during passive or active stretch, which could be valuable in assessing contracture severity and response to therapy. MRI and MR spectroscopy have been used to measure muscle volumes, fascicle length, pennation angle, fat accumulation, edema, fibrosis and remaining contractile tissue. Other MR techniques such as magnetization transfer, spin-lattice relaxation in the rotating frame (T1rho), diffusion tensor imaging and the use of contrast agents may provide more information about contracted muscle.

As described above, defects in the regulation of sarcomere number and length may contribute to contractures. A method for measuring sarcomere length using laser diffraction in CP patients undergoing surgery has provided valuable information.[17] With this method the A-bands within muscle fibers act as a diffraction grating to incident laser light, and diffraction spacing represents sarcomere length. The technique currently requires access to muscle by incision, but work is underway to adapt this technique to a needle/small probe.[18] Further development and research application of contracture-relevant outcome measures and biomarkers is anticipated.

Therapeutic Strategies

Discussions of therapeutic strategies for contractures addressed mechanical treatments (stretching, splinting and surgical lengthening) as well as pharmacologic approaches. Data were presented from a large natural history study in DMD revealing that 87% of individuals utilize stretching for contracture prevention or treatment, with or without use of orthoses (Willcocks, R. unpublished results). Even though stretching increases muscle extensibility, stretching regimens performed over periods of months appear not to have clinically important effects on joint ROM.[19,20] Increases in muscle extensibility after stretching programs up to eight weeks may be due to decreased perception of pain from stretching, resulting in acceptance of greater torque application.[21] Beneficial physiological effects of stretching unrelated to ROM, such as changes in blood flow to the muscle or decreased discomfort have not been adequately studied. In addition, the effectiveness of stretching regimens carried out over longer periods is unknown.

Non-surgical treatments with the goals of improving or preventing further loss of joint ROM also include serial casting and night splints in children with DMD or spasticity.[22,23] Better understanding of the effects of these treatments on muscle and tendon architecture through studies using ultrasound or MRI may lead to enhancements in their efficacy.

An important perspective was presented at the meeting by the mother of a young man living with DMD. She described her son's struggles when attempting to comply with recommendations for daily stretching and the use of orthotics to prevent contracture development. While parents are willing to do whatever will help their child, she asked that experts prescribe regimes based on their professional judgement and the best available information. Physicians and physical therapists should inform patients of the uncertainty of whether these conservative treatments can prevent or affect contracture progression.[19,20]

Surgical interventions for contractures focus on helping patients maintain function and comfort. Two studies were presented on outcomes after transverse gastrocnemius-soleus recession for equinus gait in children with CP.[24,25] Each showed statistically and clinically significant benefits when targeted to appropriate patients. For DMD, there is consensus that foot or Achilles tendon surgery may improve gait in ambulatory boys with significant ankle contracture who have maintained proximal lower limb strength.[26] Ambulatory boys who have severe ankle contractures tend to have insufficient strength to warrant surgery. Surgery for contractures in non-ambulatory DMD patients is not recommended except to address pain or improve wheelchair positioning.[26]

Several drugs or biologics were discussed that are being explored for their effects in preventing or treating contractures. Studies in animal models of contracture suggest that hyaluronan accumulation in the ECM may alter the viscoelastic properties of muscle contributing to contracture.[27] Results were presented from a preliminary study of treatment with intramuscular hyaluronidase, an enzyme that degrades ECM hyaluronan in patients with upper limb muscle stiffness and spasticity after cerebral injury who were at risk of developing contractures. This study demonstrated reduced muscle stiffness and increased passive and active joint movement, which persisted 3–5 months after treatment.[28] Recent work shows imaging evidence of hyaluronan accumulation in patients with muscle stiffness after cerebral injury, which changes after treatment with hyaluronidase.[29] Also discussed was the follistatin analog FST-288. When injected intramuscularly in combination with stretching in a mouse model of immobilization-induced contractures, this compound promoted longitudinal muscle growth.[30]

Research on strategies to address contracture-associated defects in muscle regeneration were also discussed. Satellite cell-derived myoblasts cultured from contracted muscle of CP patients exhibited reduced fusion and DNA methylation-dependent inhibition of pro-myogenic signaling pathways. Studies demonstrated that 5-azacytidine, a drug that alters epigenetic programming, largely reversed the fusion deficits of CP myoblasts and restored gene expression patterns consistent with pro-myogenic states.[11] Further characterization of the defects in muscle and connective tissue cell types in contractures may lead to novel drugs or biologics for contracture prevention or treatment.

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Abbreviations

CP	cerebral palsy
CMT	Charcot-Marie-Tooth disease
DMD	Duchenne muscular dystrophy
ECM	extracellular matrix
EIM	electrical impedance myography
LMN	Lower motor neuron
ROM	range of motion
T1rho	spin-lattice relaxation in the rotating frame
UMN	upper motor neuron

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Future Directions

Discussions at the meeting identified areas of ongoing and future research that may contribute to the level of understanding of contractures needed to advance prevention and treatment strategies.

To better understand the mechanisms of contracture development, additional studies are needed on:

- The changes in muscle, tendon and joint tissues leading up to and associated with contractures using available technologies including MRI, ultrasound, or EIM to determine fascicle length, pennation angle and sarcomere number and length, muscle and tendon biomechanical properties and ECM composition in the conditions for which these parameters have not yet been analyzed.
- Proliferative and regenerative capacity or fibrotic potential of progenitor cells in muscle and tendon associated with contractures.
- Neurologic activity contributing to spasticity, weakness, altered proprioception, joint pain and loss of dexterity that are predictors of contractures.
- Developing improved animal models of contracture or understanding what makes existing models of disease resistant to contractures.

To better understand why some patients develop contractures early and others do not develop contracture until much later or not at all, additional studies are needed of:

- The genetic factors associated with contractures within the same musculoskeletal or neurological condition, and across different conditions.
- Environmental factors such as level of activity/static positioning, pain management, and the effects of long term stretching and other physical therapy regimens.
- Prognostic and disease progression biomarkers based on imaging, musculoskeletal tissue composition, electrophysiological measures, biomechanical properties, or body fluid biomolecules.

Knowledge gained through these research avenues can inform the optimization of existing surgical and non-surgical treatments to lessen the impact of contractures and these studies may identify targets for the development of novel treatments or preventative measures.