Cerebral palsy (CP) is the most common cause of spasticity and physical disability in children. Muscle overactivity from chronic spasticity appears to result in increased passive muscle stiffness. This stiffness results in loss of passive range of motion (PROM) and may be a major factor in physical function as children with CP grow into adulthood.

“Excessive muscle stiffness in children has great implications for functional development into adulthood,” explains Joline E. Brandenburg, M.D., of the Department of Physical Medicine and Rehabilitation at Mayo Clinic in Rochester, Minn. “Too much stiffness can lead to deformity and decreased function.”

Passive muscle stiffness is the resistance of the muscle-tendinous unit to change length — the stiffness felt when executing range-of-motion activities. Too much stiffness may affect muscle contraction coordination and muscle activation, and it can also lead to limits in range of motion and contractures or bony deformity. “We know that muscle force is influenced by length of muscle,” explains Dr. Brandenburg. “So if the muscle is shortened by stiffness, this stiffness limits the force that can be generated.”

When comparing children who have CP with typically developing age-matched children, one study noted that it took three times more force to stretch the calf muscle in children with CP than in typically developing children. Using muscle biopsy, other researchers have observed that spastic muscles are stiffer and that the content of these muscles is different. The muscles of children with CP have an increase in collagen in the extra-cellular matrix, an increase in sarcomere length and fewer sarcomeres in series. All of these differences may affect the ease with which muscles can be stretched.

Therapeutic interventions for PROM are geared toward managing spasticity, with many focusing on the muscle or the neuromuscular junction. These include stretching, serial casting and botulinum neurotoxin. “While some improvement of muscle PROM after BoNT treatment has been observed, several recent studies have shown that BoNT does not act directly on the muscle and affect muscle stiffness, and others have offered mixed reviews of BoNT’s effects on muscle function,” explains Dr. Brandenburg.

Mayo Clinic researchers are currently investigating the use of an ultrasound elastography technique called shear wave ultrasound elastography (SWE) to quantify passive muscle stiffness in children with cerebral palsy before and after BoNT injections.
One of the problems that researchers encounter when attempting to evaluate the effectiveness of therapeutic interventions for muscle stiffness is the lack of precise measuring tools appropriate for use with children in the clinical setting. Clinical measurements of PROM and spasticity scales can provide some information, but they can yield imprecise and subjective information. Obtaining an accurate measurement of passive muscle stiffness noninvasively in the clinical setting would help providers monitor the effect and duration of effect of interventions such as BoNT, thereby guiding treatment.

Dr. Brandenburg and Mayo colleagues are currently studying the use of an ultrasound elastography technique called shear wave ultrasound elastography to quantify passive muscle stiffness in children with CP before and after BoNT injections. This technique uses a commercially available, Food and Drug Administration-approved ultrasound machine that is equipped with a probe that generates shear waves in tissue. Shear waves are generated by ultrasound push beams. These shear waves are tracked by pulse-echo ultrasound and measured using computer algorithms. This calculation provides a quantitative measure of stiffness that is based on how quickly the shear waves move through the tissue, the density of the tissue and the area of tissue measured.

The Mayo team is using this technique in an ongoing study of muscle stiffness patterns in the gastrocnemius muscles of typically developing children and children with CP undergoing treatment with BoNT. Using EMG to monitor muscle activity, researchers gently stretch the children’s calf muscles, measuring the stiffness of the gastrocnemius muscle at varying positions (Figure). Although they are still recruiting subjects and collecting data, the preliminary findings from this research are pointing to the following conclusions:

• Laxity and muscle stiffness is different in children with CP.
• BoNT appears to have a minimal effect on muscle stiffness and in some cases may have a rebound effect.
• Loss of treatment efficacy may be detected by the absence of significant change in muscle stiffness.
• Muscle activation among research subjects must be controlled because it can influence measurements of passive muscle stiffness.

Dr. Brandenburg is hopeful that by providing “target” levels of normal passive muscle stiffness, this research may help identify effective spasticity management strategies and guide timing of use of these strategies for children with CP.

Most adult humans achieve peak muscle mass sometime during their early 40s. After that point, a gradual deterioration begins. The progressive loss of skeletal muscle mass that accompanies aging (sarcopenia) and disease (cachexia) can impair muscle performance, physical function and whole-body metabolism.

The declines in physical function and mobility associated with sarcopenia and cachexia can lead to falls, loss of independence, institutionalization and even death. Given the severity of these outcomes, current research seeks to gain a better understanding of the biology of sarcopenia and cachexia and initiate development...
of therapeutic interventions to prevent, slow or reverse their progression.

The biological mechanisms underlying sarcopenia and cachexia are not well-understood. But researchers have established that multiple factors play a role, including age-associated hormone changes, sex steroids, physical inactivity, inflammation, and comorbid conditions such as heart failure, cancer and diabetes.

“Without question, exercise is the most powerful intervention to address muscle loss, whether it occurs in the context of advancing age or debilitating chronic or acute diseases,” explains Nathan K. LeBrasseur, Ph.D., of the Department of Physical Medicine and Rehabilitation at Mayo Clinic in Rochester, Minn. “However, researchers are also searching for pharmacological therapies to help improve skeletal muscle mass among people who are bedbound or unable to exercise for other reasons.”

The discovery that the growth and differentiation factor-8 (GDF-8), also known as myostatin, functions as a potent negative regulator of muscle growth has led to the exploration of whether it can serve as a mediator of sarcopenia or cachexia and as a therapeutic target. Researchers have observed that deletion and loss of function mutations in myostatin cause an increase in the number of skeletal muscle fibers (skeletal muscle hyperplasia) and an increase in the size of skeletal muscle fibers (hypertrophy). These observations have led to the hypothesis that myostatin inhibition could serve as a means to attenuate or reverse skeletal muscle mass loss in patients affected by sarcopenia, cachexia and genetic disorders such as muscular dystrophy.

Measurement of myostatin abundance is difficult, and the fact that this measurement may or may not reflect its activity further complicates the picture. “Recent research has yielded disparate findings about the relationship between age and the abundance or activity of myostatin, and about whether myostatin is a primary driver in sarcopenia,” says Dr. LeBrasseur. “More-advanced techniques to quantify the mature (biologically active) and inactive forms of this factor will need to be developed before we can draw clear conclusions about myostatin’s true role in sarcopenia.”

Dr. LeBrasseur and colleagues are currently developing the methodology to precisely measure myostatin, and they have started analyzing the data obtained from testing in 240 subjects.

### Exploring myostatin’s therapeutic potential

It’s true that myostatin’s expression and activity patterns during aging are incompletely understood. However, recent research has highlighted...
several characteristics that make it a promising therapeutic target for sarcopenia:
• Myostatin inhibition, even partial reductions, increases muscle mass in adult and older mammals.
• Myostatin’s effects are highly specific to muscle mass.
• Disrupting myostatin signaling may also positively affect multiple other age-associated changes, including increased bone mineral density, improved cardiac ejection fraction, and resistance to diet-induced obesity, dyslipidemia, atherogenesis, hepatic steatosis and inflammation.
• Myostatin is a highly druggable protein because it is secreted and accessible in the circulation.

Researchers are investigating the use of antibodies, propeptides, interacting proteins and soluble decoy receptors to inhibit myostatin activity. “Several studies offer evidence that while multiple strategies do inhibit myostatin, their safety, specificity and effectiveness differ,” explains Dr. LeBrasseur. Studies in mice and humans using a soluble decoy receptor of myostatin as an anabolic intervention, for example, have demonstrated some negative side effects.

Dr. LeBrasseur notes that while these and other studies have provided promising results, future research needs to establish the optimal way to inhibit myostatin and safely increase muscle mass.

For more information