Sports Related Neuromuscular Disorders

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Sports Related Neuromuscular Disorders

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Authors had nothing to disclose.

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Sciatica in Athletes
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Stingers and Burners
Lawrence W. Frank, MD

Upper Extremity Mononeuropathies
Andrew H. Dubin, MD, MS

Mononeuropathies of the Lower Extremities in Sports
Francis P. Lagattuta, MD

CME Activity and Faculty Evaluation

OBJECTIVES
After attending this session, participants will be able to (1) list the diagnoses associated with the presentation of sciatica in athletes, (2) distinguish on-the-field clinical characteristics of cervical radiculopathy versus brachial plexopathy, (3) understand return-to-play criteria for burner-stinger injuries, (4) formulate a differential diagnosis for nerve injuries from sports, (5) formulate an electrodiagnostic test to determine the exact nerve injury, and (6) prescribe a treatment program for the specific nerve problem.

PREREQUISITE
This course is designed as an educational opportunity for physicians.

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INTRODUCTION

Lumbar spine dysfunction among athletes presents a particular challenge to the treating physician because these patients have a high-activity level and want a swift return to their sport. Traditional treatment plans that include activity modification must consider the need for continued physical conditioning to sustain the athlete's conditioning results from months of previous sport-specific exercise. Although the long-term outcome of treatment is important, a quick return to the athlete's activity is critical. A quick return may or may not be the fastest path to the completion of treatment; shorter term treatments that will return the athlete to activity and keep them going through the season may be preferred by the athlete to a definitive treatment plan that might require more lengthy activity restrictions. The timing of the injury with respect to the specific sport season will be a critical factor in determining the type of treatment best suited to the athlete. The importance of returning the athlete to the activity, along with the sport and the athlete's position, mean that each injury is unique and challenging to the treating physician, requiring expert knowledge, keen understanding, and creativity.

The young athlete differs significantly from the adult athlete. Forty-eight percent of patients with back pain have discogenic pain. In the adolescent and young adult athlete, 47% of patients present with stress fractures, and 25% present with hyperlordosis. These presentations in young athletes may be due to several factors including the high level of mechanical stress applied to the lumbar spine in athletes, the relatively lordotic lumbar spine seen especially in young women, the immaturity of the pars interarticularis, and the relative flexibility of ligamentous structures including the annulus fibrosis.

However, sciatica occurs in the adolescent and young adult athlete just as it does in the adult athlete. Normal anatomy indicates the important role that the disc and vertebral body play in the stability of the trunk in all activities that put it at risk. Under normal conditions, the intervertebral disc carries 80% to 85% of the axial load, while the two facet joints collectively carry the remaining 15% to 20%. With forward flexion, the disc is placed at the load with the resultant torque created by the head and by objects carried increasing intradiscal pressures as high as 7 times more than in static standing. With spine extension, there is an increased percentage of weight carried by the facet joints. Degeneration of the discs or of the facet joints can result in changes in these percentages due to mechanical malalignment, pain avoidance, or instability.

PRESENTATION

Changes in training methods or intensity, inflexibility, poor technique, or poor equipment can lead to undue stress and failure of an athlete's spine-disc unit. Torsional stresses and combined motions (i.e., forward flexion and rotation) are the most injurious. Because combined motions are commonly encountered in sports, the supporting structures (i.e., muscles and connective fascia) must be of sufficient strength to offset some of the forces on the spine or the disc and facet joint complex will be vulnerable to injury. The consequences of such injury include the potential for development of facet synovitis, breakdown of the annulus, and migration of nuclear material beyond the confines of the disc and surrounding ligaments leading to mechanical or chemical irritation of nerve roots or the spinal cord. Kawakami demonstrated in a rat model that chromic gut as a chemical irrigant caused hyperalgesia, not compression. This demonstrates that although spinal nerve compression may be the primary reason for motor loss, the presence of inflammation might be the pathophysiology of pain. Similarly, an annular
sprain or annular tear without disc herniation might create a chemical environment where sciatica could occur.

For example, a 22-year-old football running back presented with a 9-month history of right buttock pain. He had dropped from second to fifth on his position depth chart. Physical examination revealed right L5 motor weakness in the hip, knee, and foot. Lumbar magnetic resonance imaging (MRI) scan revealed right L4 - L5 facet arthropathy with lateral recess stenosis and a right eccentric L5 - S1 disc herniation. Right L5 - S1 transforaminal epidural injection and L4 - L5 facet block relieved his pain and improved his strength, allowing a return to rehabilitation. When injury to another player allowed him an opportunity to play in the third week of the season, he was the team’s most valuable player, scoring two touchdowns in the victory.

Young athletes that have no spine degeneration, disc space narrowing, facet hypertrophy, or ligamentous hypertrophy have a stable segment with a wide open spinal canal. A small central or lateral disc herniation or protrusion might lead to fairly subtle symptoms rather than the classical signs and symptoms of disc herniation and sciatica commonly seen in older adults. A 20-year-old gymnast presented with bilateral lower extremity pain with uneven bar and floor exercise routines. A normal neurological examination was noted. A lumbar MRI scan revealed a broad-based eccentric disc bulge at L5 - S1 with no stenosis. Caudal epidural injection relieved her symptoms and allowed her training and competition schedule to resume.

Athletes presenting with classic sciatica symptoms may not have a readily identifiable disc herniation that corresponds with the neuroanatomic level of their symptoms. This may be due to complete annular tear without disc herniation, referred pain from discogenic causes, or nerve root injury or dysfunction that occurs due to insult from ligament or annular trauma during a ballistic activity that does not result in ligament or annular failure. Sensory loss and weakness can be insidious and unrealized, as in the example of the 22-year-old running back, resulting in significant dysfunction in high-demand athletic activities.

In adult populations, the type of activity and history of trauma are risk factors for sciatica and disability resulting from the sciatica. The increased risk in noncontact sports such as diving, golf, gymnastics, racquet sports, rowing, and weight lifting might be accounted for on the basis of activity with strain on the lumbar disc unit. This increased risk may explain the higher incidences of low-back pain and sciatica in contact sports such as basketball, hockey, football, rugby, and wrestling.

Long-term follow-up studies indicate that approximately one-third of primary care acute back pain patients continue to experience back pain for at least half of the time during the first 2 years. This suggests that with the initial insult to the spine, changes occur that render the spine damaged from the standpoint of strength, flexibility, stability, and fatigue, with resultant mechanical dysfunction and vulnerability to further injury. For the athlete, the distinction between the absence of symptoms and an absence of dysfunction is particularly important.

Differential Diagnosis

Myofascial pain with trigger points can cause referred pain that mimics sciatica. The use of trigger point injection with local anesthetic can clarify the diagnosis. In addition, trochanteric bursitis can result in lateral hip and posterior thigh pain. Treatment would include ultrasound with myofascial treatment or intra-bursal steroid and local anesthetic injection. The facet joint has been shown to cause limb pain. The mechanism of injury could include referred pain in segments with similar innervation or compression due to neuroforaminal stenosis, lateral recess stenosis, synovial cyst, or degenerative arthritis. Intra-articular injection can clarify the diagnosis, and result in effective treatment of synovitis or the synovial cyst.

Referred pain from other sources including the sacroiliac (SI) joint may also occur. The pathophysiology is referred pain in the L5 - S4 distributions or lumbosacral plexus irritability. Additionally, SI joint hypo-mobility with sacral torsion can result in nerve root irritability due to rotation of the L5 - S1 segment, further irritated by the ballistic movements demanded by athletic training and competition. Clinical testing of the SI joint has a low sensitivity and specificity. Radiological testing also has low sensitivity and specificity. Although its validity is questioned, intra-articular injection is an important diagnostic and therapeutic intervention. Intra-articular injection, medial branch blocks, and medial branch radio frequency ablation are available treatment options.

Treatment

In a Cochrane review, there was no apparent benefit of bed rest over general activity. Early treatment with spine manipulation is not recommended. There is no proven efficacy for lumbar traction in the treatment of acute low back pain. The McKenzie approach for acute disc herniation has demonstrated efficacy in selective patients with centralizing symptoms with lumbar extension. This study gives credence to the concept for posture training for a postero-lateral disc herniation in extension and a central disc herniation in mild flexion or neutral position. The patient learns how to control trunk and hip musculature to reduce forces on the supportive muscles and ligaments of the spine. The ability to maintain these correct postures may require correction of tightness in the hamstrings, hip flexors, and hip rotators. Attending to weakness of the hip extensor and abdominal muscles is also needed to teach proper biomechanics for activities of daily living as well as sports activities.

Managing pain is key in achieving a rapid progression in the exercise program. This can be accomplished via medications and/or judicious use of pain-relieving modalities. Pain medication treatment with acetaminophen or nonsteroidal anti-inflammatory drugs is recommended. Narcotic pain medication and tramadol is effective. Caution should be used when prescribing narcotic pain medication early in the treatment. A study found that when controlling for demographic data and severity of presentation, narcotic pain medication is associated with longer disability and increased cost of care.
The effectiveness of transforaminal epidural steroid injections has been noted in a previous study. Lee stated that the time course of improvement of pain was over 2 weeks. A study of 224 patients treated with epidural steroids after a disc herniation showed improvement in the measures of the Oswestry low back pain disability questionnaire for up to 3 weeks post-procedure. In consideration of the number of days of complete health achieved, the cost benefit analysis for epidural steroids was not favorable, although benefits for loss of pain, improved function, and partial return to activity were not factored into the interpretation of the results. The use of epidural steroid injections as part of a total rehabilitation program rather than as a stand-alone therapy makes sense in light of its limitations.

Cauda equina remains a disorder that requires emergent management. A recent study of 56 adults indicated that acute onset of bowel or bladder symptoms in relation to the time of operation did not influence the neurological outcome. However, bowel dysfunction at the time of presentation correlated with long-term sexual function outcome. This finding contradicts previous studies showing that management within 48 hours is associated with better bowel, bladder, and sexual function outcome. Up to 83% of cases with delayed intervention were caregiver related, indicating to physicians the importance of early recognition and management.

Outcome

Long-term outcome studies consistently report no significant differences between surgical and nonsurgical care. A prospective 10-year cohort study of nearly 500 patients showed improvement rates that were not significantly different for the surgical group (69%) than from the nonsurgical group (61%). At a 10-year follow-up visit, a larger percentage of surgical patients reported that their low back and leg pain was much better or completely gone (56% versus 40%), and were reportedly more satisfied with their status (71% versus 56%). However, work and disability status at 10 years was comparable between the two groups. Over the course of the study, 25% of surgical patients required at least one additional lumbar spine operation, and 25% of nonsurgical patients had at least one lumbar spine operation. The re-operation rate was consistent with findings in other studies.

The Spine Patients Outcomes Research Trial was a nonrandomized trial that examined 743 patients prospectively managed with conservative therapy or open surgery. It noted significant differences in pain, as measured by the Medical Outcomes 36 Item Short Form Health Survey (SF-36) bodily pain scale, and functional outcome, as measured by the modified Oswestry Disability Index, in favor of the surgical group over a 2-year follow-up period. Pain showed a mean change of 40.9 in the surgical group and 26.0 in the nonoperative group at 3 months, decreasing to 42.6 and 32.4, respectively, at 2 years. Disability index scores decreased to 36.1 for the surgical group, and to 20.9 in the nonoperative group, then decreased to 37.6 and 24.2 at 2 years. All treatment effects fell within the 95% confidence intervals and were statistically significant.

Treatments such as nucleoplasty coblation and endoscopic microdiscectomy showed efficacy in a clinical series. However, no controlled trials with a comparable control group have been conducted. In the series published, the outcomes were comparable to conservative care or traditional treatments without demonstrating any distinct advantages. Osterman demonstrated this in a 2-year prospective controlled trial that compared microdiscectomy and conservative management. There were no clinically significant differences in leg or back pain intensity, subjective disability, or health-related quality of life, although discectomy seemed to be associated with a more rapid initial recovery. Peul noted similar results in a controlled trial of 283 patients with sciatica. Although 39% of the control group went on to surgery at a mean time of 18 weeks, the perceived recovery and disability scores were no different when comparing the surgical and nonsurgical groups.

Studies have demonstrated a reduction in size of the disc herniation over time. A study of 69 conservatively treated patients re-imaged with MRI at an average of 11 months showed that 63% of the subjects demonstrated a reduction in herniation size by more than 30%, and 48% showed a reduction of more than 70%. The largest herniations showed the most dramatic decrease in size. Studies have demonstrated a reduction in size of the disc herniation over time. A study of 69 conservatively treated patients re-imaged with MRI at an average of 11 months showed that 63% of the subjects demonstrated a reduction in herniation size by more than 30%, and 48% showed a reduction of more than 70%. The largest herniations showed the most dramatic decrease in size.

CONCLUSION

Sciatica in athletes is a common occurrence and has many causes. A careful review of a patient's history and physical examination, coupled with appropriate diagnostic testing is required to diagnosis sciatica. Treatment is focused on pain management to allow for rehabilitation and a return to activity. Long-term surgical and nonsurgical outcomes are not significantly different. It is reasonable to consider early surgical treatment in athletes with persistent neurological symptoms and for those with poor pain control during conservative treatment. The time delay for return to activity with surgical treatment and the lack of difference in long-term outcome between surgical and nonsurgical patients leaves open the possibility of using conservative measures to manage an athlete through a season, if pain and neurological status can be managed. Cauda equine syndrome, however requires rapid intervention to prevent long term sequelae.

REFERENCES


INTRODUCTION

The “stinger” or “burner” is common phraseology for a phenomenon among athletes describing transient paresthesias and weakness of one upper extremity after trauma. Symptoms typically last seconds to minutes, and on rare occasions last for days to weeks. Normally, patients experience complete recovery of neurological deficits after burners. Burners may have one of two etiologies: brachial plexus injury or cervical nerve root injury. Cantu has opined that high school athletes are more likely to suffer a brachial plexus lesion, while college and professional athletes are more likely to suffer from cervical radiculopathy. Clinicians should note that trauma-associated bilateral upper-extremity tingling (burning hands syndrome) or the presence of upper and lower extremity paresthesias are ominous signs of cervical spinal cord injury.

INCIDENCE

The incidence of the burner syndrome is estimated at 2.2 per 100 players. Another study indicated that 49% of all reported injuries at two universities were of this type. As this syndrome often lasts seconds to minutes and is often ignored by athletes and coaches, under-reporting is likely.

The epidemiology of chronic burner syndrome has been noted in a seminal study performed at an electrodiagnostic (EDX) laboratory. In this study, data over 23 years was analyzed retrospectively. The review found 346 athletes reporting peripheral nerve symptoms during this time period that underwent electromyography (EMG) and nerve conduction studies (NCS). Forty athletes reporting symptoms of the burner syndrome had positive EMGs. Of the 40 athletes, 30 were American football players and 10 were wrestlers. Of note, seven athletes with electrodagnostically proven axillary nerve injury had similar symptoms and mechanism of injury as burner patients. Ninety-seven patients evaluated for brachial plexopathy or cervical radiculopathy had negative EMGs and had a particularly high incidence of shoulder injury.

MECHANISM OF INJURY

The burner syndrome typically appears after a trauma resulting in forced lateral flexion or extension of the cervical spine (Figure 1), possibly also in combination with shoulder depression. This commonly occurs in American football during tackling, or when the player becomes upended, landing on his neck and shoulder. In wrestling, forcible contact of the head with the mat may lead to similar biomechanics. Nerve injury may occur with either traction or compression of the nerve. Based on neuroanatomic features, it appears that the nerve root is more susceptible to injury than the plexus because of a relative lack of perineural tissue in the neuroforamen and tension is concentrated in a single funiculus versus the multiple funiculi of the brachial plexus.
CLINICAL ASSESSMENT

Athletes suffering from the burner syndrome may be easily identified by the watchful clinician, as they will often stand with one arm dangling at the side, perhaps holding the affected arm at the wrist or forearm. Again, bilateral arm radiation or involvement of the upper and lower extremities is an ominous sign of potential spinal cord injury, and the athlete should be immobilized and imaged without delay. Athletes should be immediately examined. Gentle palpation of the cervical spine may reveal tenderness. Cervical range of motion (ROM) is initially assessed by asking the athlete to perform flexion, extension, rotation, and side bending. Rigidity indicates cervical injury, and any arm radiation leads to a high suspicion for radiculopathy. It is unwise in the face of a potentially traumatic cervical injury for the examiner to passively range the athlete’s neck. If ROM is otherwise normal and pain-free, the athlete should be asked to assume Spurling’s position. Again, arm radiation strongly suggests a cervical radiculopathy. The examiner should also palpate the shoulders bilaterally, looking for asymmetry, fracture, swelling, or tenderness.

Neurological examination of the upper extremities includes strength, light touch sensation, and reflexes with Hoffman’s sign. In athletes with often prodigious strength, it is useful for the clinician to use leverage and bilateral simultaneous manual muscle testing in order to detect subtle strength differences. As the burner syndrome often involves C5 or C6 innervated muscle, the author has found that bilateral simultaneous manual muscle testing of the shoulder external rotators is an extremely useful initial screening test, as the examiner can easily overpower these muscles even in the strongest athletes. The presence of Hoffman’s sign, particularly when particularly brisk or asymmetric, indicates the possibility of spinal cord injury.

RETURN TO PLAY DECISIONS

Acute Burner Syndrome: On-Field Management

Athletes that experience any neck pain, limitation of cervical ROM, or neurological deficits should be removed from competition for further evaluation. In these athletes, return to play is predicated on the return of normal cervical ROM and a symmetrically normal neurological examination.

Athletes with neck pain, rigidity, restricted cervical ROM lasting more than a few minutes, a positive Spurling’s sign, and of college age or older are more likely to have cervical radiculopathy. Athletes with severe acute neck pain and rigidity should be taken off-site by emergency personnel and undergo emergent plain film radiograph (x-ray) and possibly computed tomography to search for fracture. Athletes with no neck pain or motion restrictions and of high school age are more likely to have a brachial plexopathy. This distinction is of importance in the longer term treatment and workup, but on the field this distinction does not lead to any changes in return to play criteria.

Most athletes that experience the burner syndrome have paresthesias lasting 3 to 10 seconds. Weakness may persist beyond the resolution of sensory symptoms, often lasting up to several minutes. Serial motor testing beyond the resolution of sensory symptoms is necessary to determine if the athlete is safe to return to competition.

Chronic Burner Syndrome

When symptoms of a burner persist, return to play is not possible. Persistent symptoms are unusual and a search for an etiology and prognostic information is valuable. Radiographic and EDX testing may be indicated in these situations.

Radiographic Evaluation

Athletes with persistent neck pain should receive plain x-rays of the cervical spine with anteroposterior, lateral, and flexion-extension views looking for fracture and potential instability. Cadaveric studies indicate that up to 3.5mm of intervertebral subluxation and 11 degrees of intervertebral angulation is seen with flexion and extension of normal adult cervical spines with intact ligaments. Children exhibit a greater degree of physiologic ligamentous laxity and athletes with Down’s syndrome may have nonphysiologic instability of the C1 - C2 joints leading to an increased risk of catastrophic spinal cord injury. Athletes with any suspicion of cervical instability should undergo spine surgery consultation.

Athletes with a clinical suspicion of persistent cervical radiculopathy should undergo magnetic resonance imaging (MRI) scanning. In one study, 87% of athletes with recurring burner syndrome had cervical disc abnormalities on MRI, the vast majority of these abnormalities were at the C4 - C5, C5 - C6, and C6 - C7 levels. This is compared to disc abnormalities in 20% of asymptomatic athletes and 20% in those with acute burner syndrome. Return to play criteria for athletes with cervical abnormalities includes not only full, pain-free ROM with normal neurological function, but also the absence of central spinal stenosis and the presence of cerebrospinal fluid around the spinal cord at levels with disc degeneration.

EDX Evaluation

It is likely that athletes experiencing quick resolution of their symptoms have a neurapraxic injury. EDX evaluation is unnecessary for these athletes. Based on the physiology of Wallerian degeneration as a response to nerve injury, most experts recommend EMG/NCS for athletes with persistent burner symptoms and signs at 2 to 3 weeks. Athletes experiencing symptoms and signs of the burner syndrome for greater than 72 hours are likely to have abnormal EDX testing at 4 weeks, indicating axonotmesis. The largest study of EDX findings in chronic burner patients revealed that localization is electrodagnostically difficult, with fibrillations on limb needle EMG, normal paraspinus needle EMG, and normal and bilaterally symmetric sensory NCSs. Some have advocated proximal NCSs for investigation of the burner syndrome, although this
technique is often difficult with proximal distance measurement problems and poor patient tolerance.

The presence of fibrillation potentials in a nerve root or discrete plexus distribution of has been suggested to be a contraindication to return to play, especially when seen in combination with persistent weakness. Athletes with persistent weakness and fibrillation potentials should be followed with repeat EDX studies. Symmetric muscle strength recovery in the presence of polyphasic motor unit action potentials indicates re-innervation and such athletes may return to play. The absence of a completely normal EMG/NCS examination should not used as the sole criteria for precluding athletes from returning to competition.19

RECURRENT BURNER SYNDROME

Recurrent burners bring a greater susceptibility to weakness or permanent neurological injury. Football players with multiple burners in one game or those who have frequent recurrences may benefit from high shoulder pads with a soft cervical roll to help limit neck ROM.3 Such collars have been shown to decrease the mechanical load on the cervical spine.16 In addition, proper coaching and tackling techniques may decrease recurrent episodes as well.

CONCLUSION

As burners are neurological injuries resulting from trauma to the neck and shoulder, physicians must recognize the characteristic natural history of this condition to avoid further injury and for return to play decisions. Physicians must also consider an extensive differential diagnosis for players with unusual or persistent symptoms, as the consequences of releasing athletes back to competition with cervical spine disease may be potentially catastrophic. In such cases, a number of diagnostic measures including physical examination, imaging and electrodiagnostic tests are utilized in order to determine readiness to return to sports activity.

REFERENCES

INTRODUCTION

Throwing injuries have been in existence as long as human beings, rocks, and projectiles have had the opportunity to interact with one another. Classically, if one gives a child a rock, he or she will invariably find a window to throw it through or another child to throw it at. With continued growth of athletic participation, there has been a progressive increase in sports-related neurological disorders. Throwing injuries, both neurological and non-neurological, continue to rise. In the throwing athlete, extreme forces that are generated across joints during a throwing motion typically cause nerve injuries to the throwing arm. The most significant forces seen across joints occur across the elbow and shoulder joints, respectively.

MECHANICS OF THROWING

The analysis of a basic throwing motion reveals that the mechanics of throwing can be divided into five stages or phases. The first phase is classically referred to as the wind-up. The second phase is the cocking phase. The third phase is referred to as the acceleration phase. Phase four combines both the release of the object that is being thrown, and the deceleration phase of the throwing limb. The fifth and final phase is the follow-through.

Looking at each component phase in isolation, it becomes evident that the phases are intimately interrelated and are best viewed as a kinetic chain. Phases one and two, the wind-up and cocking phase, actually serve as a functional group to initiate force generation, and orient the force vector. In essence, in these phases, the human body is being wound up like a progressively coiled spring. Phase three, the acceleration phase, is the phase in which the spring is now uncoiled. In addition to the release of energy as the spring is uncoiled, phase three adds an acceleration component that in essence, adds a whip-like movement to the body and throwing limb, further multiplying the force that was generated during the wind-up and cocking phases. Phase four, the release and deceleration phase, is actually the most dangerous or potentially hazardous phase in the entire throwing cycle. It is the sequence where massive eccentric forces are transmitted through the rotator cuff in an attempt to maintain the humeral head within the glenoid fossa. Failure of the rotator cuff in eccentric loading can lead to catastrophic events and consequences. Phase five, or the follow-through, is the terminal part of the deceleration phase. By this point, the damage has already been done. The follow-through component of the throwing cycle merely serves as a way to finally dissipate whatever residual forces were left in the system.

The straightforward analysis of the different phases of the throwing cycle begins to lay the framework for an appreciation of how complex the body’s response is in terms of modulating and controlling forces across multiple joints. The ability of the throwing arm and shoulder to tolerate rapid eccentric loading is critical in maintaining the integrity of the throwing arm. Failure in phase four, or the release and deceleration phase, differentiates between the careers of a pitcher who had a successful 25-year major league baseball career, versus a 1-year wonder, who disappears after a single season, secondary to shoulder pathology.

In the discussion of the sub-phases of the throwing motion, eccentric loading is the single most significant factor to consider. By definition, eccentric loading is a phenomenon where muscle generates tension while being lengthened by the application of an external force. The energetics of eccentric loading occurs when myosin and actin cross links are forcibly torn as the muscle is being lengthened. It is a very energy efficient form of muscle action in that it does not require the continual supply of adenosine triphosphate (ATP). Given the fact that rapid eccentric loading
has been classically shown in biomechanical studies to produce the greatest forces at muscle tendon junctions and across joints, it should come as no surprise that rapid eccentric loading is, in fact, the major etiology of injury in the throwing athlete both for neurological and non-neurological injuries.

A basic review of physics further guides the understanding of the principles of force, acceleration, and torque, and how these principles apply to the throwing athlete. Newton’s first law of physics is the law of inertia. It states: a body continues in its state of rest or uniform motion unless an unbalanced force acts on it. The property of an object that causes it to remain in its state of either rest or motion is called its inertia. Because of inertia, force is needed to change the velocity of the object. The measure of inertia or the body’s resistance to change in motion is its mass. Phases one and two of the throwing cycle are the phases that introduce an unbalanced force on a ball. The introduction of an unbalanced force, namely the wind-up and cocking phase, are what initiate the movement of the ball and orient it in its ultimate direction.

Newton’s second law is the law of acceleration. It proclaims that the acceleration of an object is directly proportional to the force causing it, that the acceleration moves in the same direction as the force, and that it is inversely proportional to the mass of the object. The velocity of a pitched ball reflects the force with which the ball is thrown. It moves in the direction of the line of force at the moment of release. Newton’s second law links phase three and phase four. The mathematical construct allows for an understanding of the interrelationship between force, mass, and acceleration, which can easily be written as the formula F=ma. Converting this to biomechanical principles, the concept of impulse or the force which is utilized to move an object, can be looked at as the application of the force multiplied by a time function. In this new formula, Force(t) is equal to the mass of the object and the change in the velocity of the object over time where V final -V1 or V initial, the change in velocity over a given time interact as acceleration (F(t)= m x V(f)- V(i)/ t).

Newton’s third law is the law of reaction. It clearly states that an object at rest exerts a downward force on the substrate that it is resting upon. A classic example of this would be a book that is lying on a table exerts a downward force on the table because the book is stationary and an equal and opposite force is acting on the book. As a result, there is no motion because the forces are equal, opposite, and are balanced. Newton’s third law is clearly related to the first law that says in order to get an object moving or to change its velocity, one must apply an unbalanced force. This clearly reverts back to the first two phases of the throwing cycle where the introduction of an unbalanced force generates the initial movement of the ball.

Considering these three classic laws, one can now look at the concept of rotational equivalents and how they relate to Newtonian physics. The concept of rotational equivalents introduces the idea of torque. Torque is related to the application of the force over the length of the perpendicular momentum. In this instance, the perpendicular momentum is the length of the limb segment that is being used to throw the ball, namely the arm. It is the length of the limb segment and how it articulates with the shoulder, multiplied by the length of the body and the forces that are applied through the body and limb that relate to the concept of torque. Understanding these four concepts and the phases of throwing clearly helps explain why softball pitches not only generate more force than baseball pitches, but also interestingly enough, have a dramatically lower incidence of injuries. Understanding these principles allows an analysis of the various nerve injuries seen in the throwing athlete.

UPPER EXTREMITY NERVE INJURIES

A review of the literature describes injuries to various nerves in the upper extremities. Some injuries prove to be more common than others. Nerves that have been noted to be injured in the throwing athlete include the axillary nerve, suprascapular nerve, musculocutaneous nerve, and the ulnar and median nerves. There have been reports of injury to the long thoracic nerve, as well as the spinal accessory nerve. However, these injuries are much less common in the throwing athlete than in athletes that engage in weightlifting or wrestling activities.

Axillary nerve injuries

Axillary nerve injuries are commonly seen in athletes following an anterior shoulder dislocation. The literature reports an incidence ranging between 9% and 20% in individuals who sustained an anterior shoulder dislocation. Interestingly enough, with an inferior shoulder dislocation, the rate of axillary nerve injury climbs as high as 60%. In throwing athletes, chronic axillary nerve compression is the more classic cause of axillary nerve injury. Axillary nerve compression typically occurs in the throwing athlete at the level of the quadrilateral space. The onset of symptoms tends to be insidious as it is a progressive and compressive neuropathy. It is not typically associated with trauma. On surgical evaluation in refractory cases, it has been noticed that fibrous bands of the inferior edge of the teres minor appear to form a compressive-type structure. This has been implicated in the etiology of axillary nerve compression. Typically the compression occurs when the involved arm is in the abducted, externally rotated position, or in the throwing position. Complaints may include a sensation of tenderness in the posterior shoulder at the level of the quadrilateral space. Athletes will also complain of a sensation of positional weakness of the shoulder, deltoid atrophy, and rarely, an altered sensation in axillary nerve distribution. By far, the most common finding on physical examination is focal tenderness in the region of the posterior shoulder at the level of the quadrilateral space.

Electrodiagnostic (EDX) evaluation is critical in helping to differentiate an axillary nerve neuropathy from the C5 - C6 radiculopathy or upper trunk versus posterior cord plexus lesion. Above all else, a good physical examination is the most critical aspect of the evaluation. EDX testing should never supersede a physical examination and in fact, a meticulous examination will invariably differentiate between an axillary nerve neuropathy from a C5 - C6 radiculopathy versus a plexus level injury. Treatment for chronic axillary nerve compression is usually conservative. A review
Suprascapular Nerve Injuries

Suprascapular nerve injuries can also be seen in the throwing athlete. The typical mechanism of injury in the throwing athlete is a combination of cross body abduction and/or scapular protraction with forward flexion. This is a fairly classic body posture of the throwing athlete and manifests during the deceleration and release phase as well as the follow-through phases of the throwing cycle.

Similar to axillary nerve injuries, suprascapular nerve injuries tend to present in an insidious fashion. Complaints include vague posterior shoulder pain, weakness of abduction, and external rotation. Atrophy of both the infraspinatus and supraspinatus can be seen along with isolated infraspinatus atrophy. Whether both spinatii are involved, or atrophy to the infraspinatus is seen in isolation depends upon the level of entrapment and compression of the suprascapular nerve. The needle electromyography (EMG) examination is critical in localization of this neuropathy. Of particular importance is that the major differential diagnosis in the suprascapular nerve injury is a significantly more common injury, namely a rotator cuff rear. Rotator cuff tears are significantly more common than suprascapular nerve neuropathies and must be aggressively evaluated and treated. Management of the suprascapular nerve injury includes rest, utilization of nonsteroidal anti-inflammatory drugs, and in more refractory cases, steroid injection at the level of the suprascapular notch. Suprascapular nerve compression secondary to a cyst can be seen in a degenerative shoulder. Surgical decompression may be required. In the given scenario, there is a structural, mechanical etiology to the nerve entrapment. Historically, conservative management has a poor outcome in this patient population subset. Even after successful surgical decompression, atrophy of the spinatii may persist. Persistence of atrophy does not preclude the return of throwing activities provided the throwing athlete is asymptomatic when he or she is throwing.

Musculocutaneous Nerve Injuries

Musculocutaneous nerve injuries, while not common in the throwing athlete, have been reported and typically occur during the throwing cycle when the musculocutaneous nerves stretch across the humeral head or coracoid. Musculocutaneous nerve neuropathies typically present with biceps and brachialis atrophy and involve associated weakness of elbow flexion. It may be difficult to discern elbow flexion weakness in the well-conditioned athlete, particularly if the athlete has a well-developed brachioradialis and only has a partial injury to the musculocutaneous nerve. In this scenario, in an attempt to isolate biceps and brachialis function, the athlete should be asked to perform elbow flexion activity with the forearm in a fully supinated posture. This will isolate, from a biomechanical standpoint, the biceps and brachialis as the primary flexors of the elbow and relegate the brachioradialis to its much more tertiary role as an elbow flexor. Should elbow flexion be performed with the forearm in a pronated state or with the forearm in a neutral state, elbow flexion weakness may easily be overlooked. In this position, the brachioradialis functionally becomes the primary elbow flexor. The major differential diagnosis to distinguish from an injury to the musculocutaneous nerve is that of a rupture of the distal biceps tendon at the level of the elbow. In both cases, the athlete will present with weakness of elbow flexion; however, in the case of a rupture of the distal biceps tendon at the level of the elbow, there will be associated loss of contour of the muscle belly. In general, musculocutaneous nerve neuropathies in athletes resolve spontaneously and do not require surgical intervention. The literature implies that surgical intervention is typically associated with poor outcome and with an increased incidence of sensory dysesthesias in a lateral antibrachial cutaneous distribution.

Ulnar Nerve Injuries

Of particular interest and concern in the throwing athletes are injuries to the ulnar nerve. These classically occur at the level of the elbow and are commonly associated with concomitant injury to the ulnar collateral ligament. Refractory pain at the level of the elbow in the distribution of the ulnar collateral ligament should engender detailed analysis and evaluation of the ulnar nerve. When a throwing athlete sustains significant injury to an ulnar collateral ligament, there is a high likelihood that there has also been at least a partial injury to the ulnar nerve at the level of the elbow. A common mechanism of injury in throwing athletes in regards to ulnar nerve injury is repetitive, low-grade trauma with stretching and compression of the ulnar nerve at the level of the elbow. EMG studies in this scenario are invaluable for localizing the lesion, assessing acuity versus chronicity, and are also helpful in determining the potential for recovery. It is critical in an ulnar nerve injury that EDX testing be utilized to help differentiate ulnar nerve neuropathy at the level of the elbow from true neurogenic thoracic outlet syndrome as described by Wilburn.

Median and Radial Nerve Injuries

A review of the literature reveals a rather interesting phenomenon that has been described by several sports medicine physicians. The term “the pitchers arm” was coined after Long and colleagues observed abnormalities of sensory nerve action potential amplitudes (SNAPs) among many pitchers. As part of the study, the group obtained data on numerous pitchers who have been evaluated for complaints of neuromuscular symptoms. Repeatedly, it has been observed that abnormal SNAPs in pitchers’ throwing arms are seen independent of presenting symptoms. Of particular concern is that these abnormalities have been observed even when symptoms have been in the nonthrowing arm. This has typically been described in high-level throwing athletes and is believed to potentially represent an element of chronic recurrent low-level stretch at the level of the brachialeplexus, given the diffuse involvement of multiple SNAPs. The major implication for this scenario, however,
is one of data over-interpretation and misdiagnosis. As such, Long and colleagues recommended that an isolated study not be used as the sole determinant for nerve injury in the throwing athlete. In fact, several authors recommend the use of serial studies to determine, over time, if there is a trend towards worsening nerve parameters in EDX testing before establishing the diagnosis of nerve injury. It is the contention that the use of serial studies in determining trends are more appropriate and may help avoid unnecessary treatment and potentially invasive interventions.

Median nerve and anterior interosseous nerve neuropathies are quite uncommon in the throwing athlete. In a general population, the most common median nerve neuropathy is carpal tunnel syndrome (CTS) or median nerve compression at the level of the wrist. However, this is an uncommon finding in the throwing athlete. When examining the anatomic course of the median nerve, a median nerve injury at the level of the shoulder or upper arm is a very rare. Pitchers, however, can develop median nerve compression at the level of the pronator teres secondary to eccentric muscle trauma to the pronator teres. As a result of eccentric trauma to the pronator teres, subsequent swelling and transient median nerve compression can result. The classic mechanism of rapid eccentric loading and trauma to the pronator teres is seen in a pitcher that is working on a curve ball and has less than optimal mechanics. EMG examination in this scenario can be helpful in distinguishing median nerve neuropathy at the level of the pronator teres and more classically described CTS. On clinical examination, there may be significant symptom overlap between CTS and pronator teres syndrome.

Radial nerve neuropathy, secondary to true entrapment, is rare. Also rare is recurrent radial nerve trauma, secondary to repetitive limb use. Isolated posterior interosseous nerve neuropathies; however, do occur and have been described at the level of the arcade of Frosh. This is a fibrous band between the two heads of supinator. Classic posterior interosseous nerve neuropathies in the throwing athlete at the level of the arcade of Frosh have been believed to occur secondary to edema, synovitis, ganglion, or lipoma formation. All of these are believed to serve as compressive forces on the posterior interosseous nerve. Eccentric injury to the supinator, classically seen in screwball pitchers, can cause a posterior interosseous nerve neuropathy. EDX evaluation including needle EMG and nerve conduction studies help distinguish between a true posterior interosseous nerve neuropathy versus a radial nerve neuropathy proximal to the level of the arcade.

**Brachial Plexus Injuries**

Multiple nerves can be involved in throwing athletes. Some nerves, such as the ulnar nerve, are more commonly involved than others. There are significant ramifications with ulnar nerve involvement given the fact that it supplies the hand intrinsics of the throwing arm. As such, a detailed analysis of the function of the ulnar nerve is necessary in all pitchers.

Brachial plexus injuries are typically more commonly associated with traumatic events such as rapid downward compression of the shoulder complex, hyperabduction or overhead traction. Chronic recurrent stretch and compression may occur, particularly if the throwing athlete happens to have underlying anatomic anomalies such as a cervical rib. Generally, brachial plexus level injuries are uncommon unless there is an occurrence of an associated sudden stretch. Sudden stretch injuries to the brachial plexus in throwing athletes have been described in weight-throwing athletes (e.g., shot putters, and discus throwers). This injury is classically seen in novice weight throwers who have yet to develop sufficient shoulder and trunk musculature bulk to protect the shoulder and underlying plexus structures.

In cases of brachial plexus injuries from sudden stretch, one of the more common complaints is classically described as the stinger or burner. This typically refers to the sudden onset of circumferential paresthesias and dysesthetic pain throughout the upper limb and hand and may be associated with flaccid paresis. This tends to occur in association with a downward force on the shoulder and is sometimes accompanied by lateral flexion of the head or neck to the opposite side. This has been well described in football tackling, but it can also occur in the weight-throwing athlete. A shot putter learning a spin technique, novice discus throwers, or novice shot put gliders are at a high risk.

Multiple nerves can be involved in the throwing athlete. For illustrative purposes, two cases are presented for review.

**CASE DISCUSSIONS**

The first case involves a 17-year-old female shot putter. She is a nervous thrower with noted weakness and currently lacks sufficient shoulder strength. She is a glider as opposed to a spinner. Both gliders and spinners require significant amounts of strength, but gliders need even more strength than spinners. Spinners typically generate their linear throwing forces through torque development. This effectively converts shot putting to a speed as opposed to a strength activity. The patient developed right arm pain after throwing in a tournament. She experienced immediate paresthesias in the entire arm with a sensation of weakness. By description, she had a burner or a stinger. Her primary physician initially diagnosed her as having sustained a shoulder sprain. The patient noted that activities such as bench pressing worsened her pain. Her physical examination showed no evidence of muscle asymmetry. This is important because a weight thrower should be asymmetric, with the dominant throwing arm hypertrophied, relative to the nondominant arm. A sensory examination revealed decreased pin sensation in the right thumb and index finger involving both the dorsal and palmar surfaces and altered sensation in the lateral forearm. She was noted to have weakness in the deltoid, biceps, and pronator teres as well as in the wrist extensors. Triceps were noted to be strong. Differential diagnosis included transient stinger or burner, C6 radiculopathy, plexus level injury, musculocutaneous nerve neuropathy, and possibly even CTS. Rank ordering of the differential diagnosis placed plexopathy versus C6 radiculopathy as the highest likelihood. EDX testing revealed on the right, a small lateral antebrachial cutaneous SNAP, and a small radial
SNAP. Motor nerve conduction studies revealed a small right musculocutaneous to biceps compound motor action potential (CMAP). Needle EMG examination showed evidence of active denervation in the deltoid, biceps, extensor carpi radialis longus, and pronator teres with an unremarkable triceps and unremarkable paraspinals. Clearly in this scenario, the patient has an upper trunk level brachial plexopathy.

Case 2 involves a 23-year-old professional baseball player. He is an AA outfielder for a local baseball team. He had a history of rotator cuff repair that was performed 18 months prior with anchor fixation and good outcome. History reveals that he developed right shoulder pain after playing long toss in the outfield with a teammate. He did not have acute pain during the throwing activity, which would suggest it was not acute rotator cuff pathology. He noted the development of pain the day after throwing. Shortly thereafter, he noticed altered sensation in the thumb, index finger, and long fingers of the right hand. The patient noted weakness of the right triceps and a dramatic loss of strength during bench press activities. His physical examination was significant for rather profound triceps atrophy, and loss of the triceps reflex. On manual muscle testing, he was noted to have significant weakness in the triceps, extensor carpi radialis longus, deltoid, as well as external rotators. The sensory examination revealed decreased sensation in the axillary nerve distribution as well as a radial nerve distribution. Differential diagnoses included cervical polyradiculopathy at the C5, C6, and C7 levels, isolated brachial plexopathy, combined axillary nerve and radial nerve neuropathy, and a combination of brachial plexopathy and radiculopathy. EMG data revealed small CMAP amplitude for the extensor indicis proprius on the right and a small right radial SNAP. Needle EMG results showed acute on chronic denervation of the right deltoid and acute on chronic denervation of the teres minor. The patient was noted to have acute denervation of the right triceps and extensor indices proprius as well as acute denervation at the C7 paraspinal level. This patient has two processes in occurrence. He has acute on chronic findings of deltoids and teres minor, which are axillary nerve and posterior cord innervated. He also has acute denervation in the triceps and extensor indicis proprius, both of which share radial nerve and posterior cord innervation. Additionally, acute denervation is noted in right C7 level paraspinals. This in concert with a small radial SNAP amplitude assists in concluding that the patient is experiencing a combination of an acute chronic plexopathy and an acute C7 radiculopathy.

CONCLUSION

The throwing athlete is a rather remarkable individual. He or she is not only able to generate tremendous forces over short periods of time, but can accurately locate these forces and translate them into horizontal vectors that allow for the accurate throwing of projectiles. It is, however, the unique capacity of the high-level throwing athlete to sum a myriad of forces to a final common pathway that ultimately exposes the overhead-throwing athlete to potentially catastrophic injury. It is imperative for physicians that care for these individuals to be fully versed in the neurological and non-neurological sequelae of the force applications that are generated by the throwing athlete.

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Mononeuropathies of the Lower Extremities in Sports

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INTRODUCTION

Kobe Bryant gets carried off the court with an ankle sprain. Most sports fans feel that the ligaments in the ankle will heal and the player will return to play as soon as possible. In some cases in grade II and grade III ankle sprains, the peroneal nerve is injured as well as the ligaments, delaying the return of the player to his team. The lower limbs are the most frequently injured body parts in sports. This is because all sports require locomotion, which is generated by the legs. Therefore, there is going to be a higher incidence of knee, ankle, and hip injuries in almost all sports. The most serious injuries are in the knees, with fewer in the ankles, and even less in the hips. The significant injuries to the lower limbs and the knee are primarily of ligaments and cartilage but in 11% of the cases, there can be nerve injuries as well.¹⁸ The nerve injuries may or may not be obvious. For the neuromuscular physician, the patient may have been referred following a workup for the muscles, ligaments, and cartilage injuries with the primary care provider or orthopedic physician. Therefore, most of the structural elements have already been evaluated, and it is the neuromuscular physician’s role to identify the nerve injury, confirm the diagnosis, and treat the injury.

FEMORAL NERVE INJURIES

Anatomy

The femoral nerve arises from the posterior divisions of the ventral primary rami of L2, L3, and L4. These nerves form the largest branch of the lumbosacral plexus. The femoral nerve merges from the lateral border of the psoas muscle. It divides into multiple branches within the femoral triangle. It divides into sensory branches in the proximal thigh to innervate the upper and anterior thigh and muscular branches to quadriceps muscles. One sensory nerve branches lateral to form the femoral cutaneous nerve. The femoral nerve also divides into the medial femoral cutaneous nerve which originates just distal to the inguinal ligament to descend on the sartorius muscle and penetrates the deep fascia. This splits into two terminal nerve branches; one branch innervates the skin covering the medial aspect of the distal thigh and knee joint region, and the second branch supplies the skin superior to the patella through several community branches with the saphenous nerve. The posterior branch of the medial cutaneous nerve also communicates with the saphenous nerve and provides cutaneous sensation to the patellar region. The saphenous nerve is also derived from the femoral nerve (Figure 1).

The femoral nerve is not commonly entrapped in sports. However, when the nerve becomes entrapped, it is in close proximity to the femoral head, the tendinous insertion of the vastus intermedius, the psoas tendon, the hip, and the joint capsule. The nerve is vulnerable in this area. In sports it may be seen with hip dislocations, pelvic fractures, and acute hyperextension of the thigh. The patients may be more vulnerable if they are diabetic, especially if their disease is not well controlled.¹⁸,²⁴,²⁹

Etiology

Femoral neuropathy has also been seen in gymnastics and in female modern dancers with the hinge maneuver. This is a hyperextension of the hips while in the kneeling position which causes a stretch injury.
Mononeuropathies of the Lower Extremities in Sports

Clinical

Clinical findings of a femoral neuropathy involve pain in the inguinal region that may be relieved from flexion and external rotation of the hip. There can be dysesthesias over the anterior thigh and anterior medial leg. Patients complain of knee buckling when walking, numbness in the distribution of the saphenous nerve, and also anterior knee pain.

On physical examination, the patient may present with weak hip flexion and knee extension, decreased quadriceps tendon reflex, and decreased sensation in the anteromedial aspect of the thigh. The pain can be increased with hip extension and relieved with external rotation. If the nerve is compressed in the inguinal ligament, there would be no hip flexor weakness since the motor branch to the hip flexors muscles is before the ligament.

Electromyography (EMG) testing may show needle changes in the muscles innervated by the femoral nerve, which is the quadriceps and the hip flexor muscles including the psoas muscle. Nerve conduc-

tion studies (NCSs) may show prolonged conduction velocity and a decreased amplitude from side to side picking up with the electrodes on the vastus medialis. A saphenous study may also be performed which would have a decreased amplitude and can be prolonged from the contralateral side. When performing the needle EMG study, it is important to look at the adductor muscles to rule out a lumbar radiculopathy as the obturator nerve is also supplied by the L2, L3, and L4 nerves. If the adductor muscles are involved, it is most likely a lumbar radiculopathy and not a pure femoral neuropathy.

Treatment

Surgical treatment for the hip and pelvis trauma may be necessary. The goal of nonsurgical treatment is to decrease the inflammation on the nerve as well as provide symptomatic treatment for pain and dysesthesias. Acute neural inflammation can be treated with a dosing regimen of oral corticosteroids, (prednisone or medrol). Intramuscular (IM) corticosteroids, as well as an injection with intravenous (IV) soluble corticosteroids, preferably ultrasound guided, can be given directly at the site of the injury. After the initial corticosteroids, nonsteroidal anti-inflammatory drugs can be given at appropriate doses for continued inflammatory control.

Symptomatic treatment for nerve pain includes such antiepileptic medicines as pregabalin and off-label use of gabapentin, carbamazepine, or lamotrigine and others that work to decrease the neural signal through calcium channel blockers. Other pharmaceutical treatment includes duloxetine and off-label use of tricyclic antidepressants through the norepinephrine and serotonin mechanisms. Topical treatments using capsaicin and topical lidocaine can also be used as an adjunctive treatment. Analgesic medicines such as tramadol and other opioids can be used in moderately severe cases. Methadone, due to its special properties with N-methyl-D-aspartic receptors, may be especially useful in severe cases. TeNS units and other physical modalities may also be used. This is called the neuropathic treatment model.

In femoral neuropathy, the quadriceps weakness may be treated with a locking knee brace and an assistive device to prevent instability. In refractory cases, 70% of patients experience significant relief with this approach or surgery. A strengthening program of the lower limbs, including proprioception, is necessary after surgical or nonsurgical treatment.

SAPHENOUS NERVE INJURY

Anatomy

The saphenous nerve is the terminal branch from the femoral nerve. The longest branch of the femoral nerves is a pure sensory nerve and is made up of fibers from the L3 and L4 spinal segments. It may become entrapped in multiple locations from the thigh to the leg. The saphenous nerve can be entrapped where it pierces connective tissue at the roof of Hunter's canal. The sharp angulations of the nerve through the Hunter's canal is under dynamic forces from the muscles in this area. Contraction and relaxation impinges the nerve.
Etiology

The saphenous nerve can be injured by a surfer who is holding a surfboard between his legs or as a complication of a runner who has swelling from pes anserinus bursitis. It can also be injured in traumatic injuries such as patellar dislocations in rugby and football. Knee surgery complications can also lead to saphenous nerve damage.6,9,11,17,18,21

Clinical

The symptoms of an entrapment include a deep aching sensation in the thigh, knee pain, and paresthesias in the distribution of the saphenous nerve in the leg and foot. The infrapatellar branch may also be entrapped as it passes through a separate foramen in the sartorius muscle tendon and courses horizontally through the prominence of the medial femoral epicondyle. Patients have reported paresthesias and numbness in the infrapatellar region, which worsens with knee flexion, or from the compression of garments or knee braces.

On physical examination, the patient should have no weakness. If there is weakness, the examining physician should consider a femoral nerve injury or a L3 or L4 radiculopathy. There should be numbness along the course of the nerve, and deep palpation proximal to the medial epicondyle may reproduce the pain.

Diagnosis can be made by an NCS with side-to-side changes as well as a local injection along the course of the nerves and proximal site of the entrapment under ultrasound guidance. Needle EMG examination should be normal. This includes all L3 and L4 innervated muscles as well as muscles that are innervated by both the femoral and obturator nerves. Additionally, the lumbar paraspinal muscles should be tested to rule out a radiculopathy.

Treatment

Entrapment in Hunter’s canal is treated with an IV soluble corticosteroid and a local anesthetic, preferably ultrasound guided. If this fails after multiple attempts, surgical decompression may be necessary. Persistent symptoms may also be treated with the neuropathic treatment model.

LATERAL FEMORAL CUTANEOUS NERVE INJURY

Anatomy

The lateral femoral cutaneous nerve consists of the L2, L3, and L4 nerves and it can be entrapped or compressed as it goes through a fibrous muscular ring through the inguinal ligament, the iliopsoas muscle, and distal femoral fascia. Meralgia paresthetica is another term used to describe this.

Etiology

Meralgia paresthetica may be caused by direct trauma such as a “hip pointer” which is a contusion to the anterior superior iliac spine (ASIS). This can occur in any contact sport such as football, hockey, soccer, or basketball. It is also seen in overuse syndromes such as jumping rope, using uneven parallel bars in gymnastics, and at times, when a weight-lifting belt is being worn too tightly.

Clinical

Symptoms of meralgia paresthetica consist of anterior and lateral thigh burning, tingling, or numbness. The pain is worsened with standing and walking, but relieved by sitting.

Diagnosis is primarily made in clinical terms, although NCSs can be performed side-to-side, comparing amplitudes and latencies (Figure 2). A needle EMG examination should be performed and found negative to rule out a femoral neuropathy or lumbar radiculopathy.19,22,27

Figure 2 Anatomy and stimulation technique for the lateral cutaneous nerve of the thigh. (Source: Johnson EW and colleagues, Practical Electromyography 1997;179.)
Treatment

Treatment for a lateral cutaneous nerve injury is an injection that uses local anesthetics and corticosteroids and can be ultrasound guided. If the injection provides complete but only short-term relief, surgical decompression or a neurolysis can be performed on the nerve. Persistent symptoms may be treated with the neuropathic treatment model.

OBTURATOR NERVE INJURY

Anatomy

The obturator nerve is made up of the L2, L3, and L4 branches. It enters the obturator canal and leaves through the obturator foramen, supplies the adductor muscles as well as gracilis and obturator externus, and may be entrapped between the muscles. 27

Clinical

The symptoms include weakness between the thigh and a sensory deficit in the inner thigh. This is seen in rugby players with chronic groin pain. The players present with post-exercise thigh pain and the injury occurs at the level of the obturator foramen. The patient may also complain that his or her ability to jump is lessened. The symptoms worsen with exercise. In severe injuries, loss of adduction and internal rotation occur, leaving the patient with an externally rotated foot. Wasting of the adductor muscles of the thigh may occur.3,4,18

Diagnosis can be made by needle EMG examination that would indicate membrane irritability in the adductor muscles which are innervated by the obturator nerve. The femoral nerve and the lumbar paraspinals would be normal. This test must be performed to rule out other causes.

Treatment

Treatments for entrapment include electrical stimulation of the adductor and hip flexor muscles, stretching, and massage. Surgery may be necessary in refractory cases. The surgery involves dividing the fascia over the pectineus and the adductor longus muscles and dissecting the space between the two muscles to relieve the anterior branch of the nerve. For chronic pain, the neuropathic treatment model is recommended.

SCIATIC NERVE INJURY

Anatomy

The sciatic nerve is made up of the anterior rami of the tibial nerve and the posterior ramus of the peroneal nerve. The sciatic nerve exits through the pelvis of the greater sciatic foramen lateral to the ischial tuberosity beneath the piriformis muscle and branches the four hamstrings before the bifurcation. The peroneal fibers provide innervation to the short head of the biceps.23 This important branch allows for the identification of a sciatic nerve lesion’s location (Figure 3).29

Figure 3 Anatomy of the sciatic nerve in the gluteal region. (Source: Johnson EW and colleagues, Practical Electromyography 1997;181.) M = muscle; N = nerve

Etiology

The main etiology for sciatic nerve injuries in sports is from major trauma. This includes falls on the buttocks, posterior hip dislocations, proximal tibia fractures and lower leg fractures, and as seen in football, direct trauma to the thigh. In addition, posterior femoral cutaneous nerve lesions can be seen with patients who are sitting on a bike, or after a hamstring tear with a complication of myositis ossificans. This can cause direct entrapment of the nerve. The peroneal division is injured more frequently than the tibial division and tends to involve more severe injuries, yet the tibial nerve heals better than the peroneal branch. 7,18,19

Clinical

On physical examination, symptoms may include weakness in the hamstrings or other symptoms relating to the peroneal or tibial nerves. Numbness in the foot and the back of the leg, as well as weakness in the dorsi and plantar flexion could also be experienced, depending on which branch is more severely injured.

Diagnosis is made by neurodiagnostic studies with classic findings involving the peroneal, tibial, and sciatic innervated muscles with a prolonged H reflex and abnormal F waves to both the tibial and peroneal nerves, as compared to the contralateral side. The paraspinals would be spared, ruling out an L5 and or S1 radiculopathy.

Treatment

The main focus for this type of injury is treating the trauma. The injured nerve treatment would focus on the peroneal or tibial component. If there is weakness of the peroneal division,
treatment is discussed below under treating common peroneal nerve injuries. Persistent symptoms and numbness can be treated with the neuropathic treatment model.

COMMON PERONEAL NERVE NEUROPATHY

Anatomy

The common peroneal nerve arises from the sciatic nerve to approximately the distal third of the thigh region. At this point, it descends to the popliteal fossa innervating the short head of the biceps femoris muscle. In the fibular head, the common peroneal gives off two branches, the sural communicating branch, and the lateral cutaneous nerve of the calf. The common peroneal nerve then courses around the fibular neck and passes through the fibrous osseous opening in the superficial head of the peroneal longus muscle. Distal to the fibular tunnel, the common peroneal divides into the superficial and deep peroneal branches. The superficial peroneal provides innervation to the peroneus longus and brevis muscles, and travels to pierce and open the deep fascia in the distal third of the anterior leg. The superficial peroneal nerve splits into the medial and lateral terminal sensory branches that pass anterior to the ankle and innervate the dorsum of the foot, except for the region between the first and second toes. The deep peroneal nerve descends along the leg between the tibialis anterior and extensor hallucis longus, innervating those muscles as well as supplying the extensor digitorum longus and the peroneus tertius muscle.

Etiology

The etiology of the common peroneal nerve would be a direct compression from a stretch injury at the region of the fibular head. This is seen in almost all sports and includes anterior cruciate ligament (ACL) tears, lateral collateral ligament (LCC) tears, and posterior cruciate ligament (PCL) tears. It can be seen in 20% of knee dislocations. Direct trauma from hockey pucks, direct blows from hockey sticks to the leg, kicking in soccer, and helmet hits to the nerve itself are also causes. It is also seen in cricket with tight bands on the uniform. Additionally, it can be seen in hematomas or compartment syndrome, grade II and grade III inversion ankle sprains, and in chronic repetitive activity such as runners with tight fascial bands or hypermobilities of the fibular head.18,19,20 It is seen in fabella syndrome, which is entrapment by the accessory ossicle in the lateral gastrocnemius muscle. It is also seen as a surgical complication with lateral meniscus surgery and as a side effect of cryotherapy after an ice bag has been taped on too tightly.

Clinical

The patient presents with an altered gait, secondary to weak ankle dorsiflexors. This could be referred to as a steppage gait. In certain cases, pain may not be present. The patient will have difficulty walking on his heels, have a noticeable foot slap on foot strike, or trip while walking.

The examination reveals a variable pattern of weakness with the extensor digitorum brevis (EDB) being affected as well as the ankle and toe dorsiflexions. Radiographs are important in the diagnosis of underlying trauma such as fibular head fracture. An ultrasound, computed tomography scan, or magnetic resonance imaging (MRI) of the knee may also be of benefit. The EDX examination is the best method for evaluating the peroneal nerve. Sensory NCSs of the superficial peroneal are performed bilaterally. If the nerve is abnormal, it implies that the lesion is distal to the dorsal ganglion and most likely not an L5 radiculopathy. Comparisons of side-to-side superficial peroneal sensory nerve action potential (SNAP) evaluates the degree of axonal loss and prognosis. Motor NCSs are performed with the active electrode on the EDB muscle. Calculation of the peroneal nerve across the fibular head is important. If the nerve conduction velocity is less than 40 ms, it is considered abnormal and side-to-side testing may be of benefit. If the compound muscle action potential is smaller from side-to-side, this may also be of benefit although the EDB may not be as reliable as other more proximal muscles. EMG is important in confirming the exact location of the nerve injury. In this situation, if the common peroneal nerve is the site of the lesion, there should be abnormalities in both the deep peroneal as well as the superficial peroneal muscles. If the short head of the biceps muscle is involved it indicates that the lesion is proximal to the fibular head. In addition, the tibial nerve needs to be examined, especially the flexor digitorum longus, to rule out an L5 or sciatic nerve injury.15,33

Treatment

In all acute nerve compromise or nerve compressions, reducing inflammation is of primary importance. Oral or IM corticosteroids can be used as well as an ultrasound guided injection that bathes the nerve at the site of the compression.

An ankle foot orthotic may be needed to be worn if severe foot drop occurs. Shoe orthotics may also be beneficial in patients with severe flatfoot or cavus foot. In a patient with a mild lesion, taping the ankle or wearing high-top shoes may allow the patient to participate in sports earlier. Electrical stimulation may be used to decrease atrophy. Surgery should not be performed unless there has been no improvement in over 4 months. Persistent sensory symptoms can be treated with the neuropathic treatment model.

DEEP AND SUPERFICIAL PERONEAL NERVE NEUROPATHY

Anatomy

The superficial peroneal nerve travels in the lateral compartment, innervates the peroneal longus and EBD muscles, and provides sensation of the dorsum of the foot. The deep peroneal nerve innervates the tibialis anterior, peroneus tertius, extensor hallucis, and provides sensation at the web of the first and second toes (Figures 4, 5, 6).
Etiology

Compartment syndromes, due to fascial defects or a neuroma, are the most common injuries to these areas. The superficial peroneal can be directly injured with tight lacing of shoes. Injury can occur in the deep peroneal nerve in a variety of ways that include the use of tight-fitting ski boots, the act of kicking a soccer ball, or by tight en pointe movements performed by ballet dancers (Figures 7a and 7b).

Clinical

The symptoms of the deep peroneal nerve injury include a vague burning sensation over the dorsum of the foot. In severe cases, there is decreased sensation in the first two toes, a first toe drop, or a patient that trips when walking. The superficial peroneal nerve injury has findings of decreased sensation and pain at the dorsum of the foot. The symptoms worsen with exercise.
Treatment

Treatment options for the deep and superficial peroneal nerves are similar to those for the common peroneal nerve injury with the added recommendation that no pressure is placed on the dorsum of the foot. Aggressive treatment with corticosteroids can be used.

Proper physical therapy, ankle-foot orthoses, and shoe orthotics may be used if necessary. Persistent symptoms should be treated with the neuropathic treatment model.

TIBIAL NEUROPATHY

Anatomy

The tibial nerve comes from the L3 to the S3 nerve roots. When the posterior tibial nerve is entrapped, it is called tarsal tunnel syndrome (TTS). It is the most common type of entrapment of the foot and ankle area (Figure 8). The nerve is a branch of the sciatic nerve and enters the leg between the two heads of the gastrocnemius. Most individuals have a single calcaneal nerve which arises from the posterior tibial nerve but sometimes may arise from the lateral plantar nerve. Twenty-one percent of people have multiple calcaneal branches originating from the posterior nerve, lateral plantar or medial plantar nerve, or a combination of the nerves. The tarsal tunnel is formed by the medial surface of the talus, the inferomedial navicular, the sustentaculum tali, and the curved medial surface of the calcaneus. The fibrous portion of the canal is the flexor retinaculum which is also called the lacinate ligament. The retinaculum is formed by the deep superficial aponeurosis of the leg, as closely attached to the sheath of the posterior tibial at the flexor digitorum longus and flexor hallucis longus. The three branches are the lateral plantar, medial plantar and medial calcaneal divisions and provide sensation to the soles of the feet (Figure 9).

Etiology

TTS is seen in runners and has been described by Rask as jogger’s foot. He theorized that the excessive valgus or external rotation of the foot during running and excessive stretch on the medial plantar nerve resulted in TTS. TTS is seen in runners with flat feet who use corrective orthotics that actually compress the nerve in the medial arch. TTS can be seen with tibial fractures or in frank dislocations of the ankle or deep lacerations that may be caused by the blade of a skate. It can also occur in runners from compression by a Baker’s cyst. The proximal tibial nerve can be entrapped by the tendinous arch of the origin of the psoas muscle. It can also be a complication of surgery of the anterior cruciate ligament repair or Achilles tendon repair. TTS is also commonly seen in mountain climbers and skiers.

Patients will present with diffuse vague discomfort or pain with burning, tingling, or frank numbness in the plantar area of the foot. Occasionally, there might be a report of proximal radiation of pain in the medial leg. Prolonged standing and walking exacerbate the symptoms while rest can improve the symptoms.
Mononeuropathies of the Lower Extremities in Sports

Figure 8 Tarsal tunnel syndrome in patient who had a prominent bony spur at the posteromedial talus following a fracture. a, b Transverse 12-5 MHz US images of the tarsal tunnel obtained a in plantar flexion and b during forced eversion and dorsiflexion of the foot. a In plantar flexion, the bony spur (arrow) is seen as a hyperechoic image which bulges in the tunnel between the flexor digitorum longus (fdl) and the flexor hallucis longus (fhl) tendons. The tibial nerve (arrowheads) is located behind the posterior tibial artery (a) and veins (v) and appears swollen and hypoechoic in comparison with its normal appearance depicted in Fig. 16.30. tp, tibialis posterior tendon. b During eversion and dorsiflexion of the foot, the nerve appears flattened and compressed against the anomalous bone. c, d The location and appearance of the bony spur (arrows) is well depicted on a c CT scan and d T2*-weighted MR image. e, f Photographs of the medial aspect of the ankle with the patient’s foot e plantar flexed and f dorsiflexed and everted. In f note the abnormal surface prominence of the spur (curved arrow). MM, medial malleolus. Source: Bianchi S & Martinoli C, Ultrasound of the Musculoskeletal System, 2007;816.

Patients also present with night pain that improves with massage or walking. It is worse with extreme dorsiflexion secondary to the nerve tension. Patients with entrapment of the lateral nerve have experience of chronic heel pain that may be present for nearly 9 to 12 months. The symptoms are similar to those of plantar fasciitis. These patients can have pain when they are weight bearing, when they are seated, and during the evening hours. Patients are usually asymptomatic in the mornings prior to weight bearing, but find that symptoms worsen with increased activity (e.g., long periods of standing, walking, or running) and toward the end of the day.

Clinical

On physical examination, the patients experience the most severe tenderness over the first branch of the lateral plantar nerve, and over the plantar medial heel under the abductor hallucis muscle. Many patients have tenderness along the entire posterior tibial nerve starting from the distal medial malleolus. Tenderness may also be present over the plantar fascial insertion in the medial calcaneal tuberosity.

Patients with entrapment of the medial plantar nerve may notice tenderness over the medial arch inferior to the navicular tuberosity and not directly over the plantar fascia, and may have Tinel’s sign at that area with prolonged weight bearing.

Differential diagnosis includes plantar fasciitis, heel spurs, plantar cellulitis, tibial sciatic neuropathy, lumbar radiculopathy, and a Morton’s neuroma.

The diagnosis is made by history and physical examination. EMG and NCSs of the medial and lateral plantar nerves can be used to confirm the diagnosis. Motor, sensory, and mixed NCSs can be performed. Needle EMG of the muscles innervated by both the medial and lateral plantar nerves is necessary. It has been reported that the accuracy of the SNAP and mixed nerve potentials are almost identical, but the SNAPs were found to be more sensitive and less specific while the mixed nerves were less sensitive and more specific. The mixed NCS is technically easier to perform and is better tolerated in patients. Approximately 90% of patients with TTS will have abnormal findings on EMG and NCSs.8

Figure 9 The tarsal tunnel and course of the tibial nerve. Source: Johnson EW and colleagues, Practical Electromyography 1997;189. N = nerve

Treatment

Treatment for TTS is directed towards the underlying etiology of neural compression.32 Nonoperatively, patients can have a trial of immobilization with the use of a cast, walking boots, and orthotic management that will relieve the postural abnormalities caused by chronic traction or compression traction to the nerve. Treatment such as corticosteroids and local anesthetic injections guided by ultrasound can also be of benefit. Chronic pain symptoms may be treated with the neuropathic treatment model.
SURAL NERVE INJURY
Anatomy

The sural nerve comes from the tibial and common peroneal nerves. It is from the S1 nerve root and it is a pure sensory nerve to the lateral part of the leg and foot.

Etiology

The etiology of injury is from direct compression from a Baker’s cyst that may include tight boots worn while skiing or skating, ankle reconstruction surgery, or a fifth metatarsal fracture. 18

Clinical

Symptomatically, the patient will have pain or numbness in the posterior leg with no weakness. Differential diagnosis includes an S1 radiculopathy or lumbosacral plexopathy.

Treatment

Nonoperative treatment is similar to treatment in the neuropathic treatment model.

Pudendal Neuropathy
Anatomy

The pudendal nerve arises from the S2 to S4 nerves.

Etiology

In cyclists, 11% to 27% experience penile numbness and up to 13% are impotent. In addition, female cyclists or those who participate in spinning classes have reported desensitization in the genital area.

Treatment

Special seat coverings, such as the Spenco seat cushion, distribute the pressure over a greater area. Conservative treatment is the neuropathic treatment model.

SPORTS HERNIAS
Anatomy

The iliohypogastric nerve arises primarily from the ventral primary ramus of L1 with a contribution from T12. The iliohypogastric nerve traverses the psoas major and pierces the lateral border anterior to the quadratus lumborum muscle. It is posterior to the kidney and transverse to the lateral abdominal wall. The nerve penetrates the transverse abdominal muscle near the iliac crest that comes between the internal oblique musculature. It supplies the lower fibers of the transverse abdominal muscle and internal oblique and divides into lateral and anterior cutaneous branches.

Etiology

The nerve is rarely injured in isolation. Surgical procedures are recognized as the most common cause, but nerve injury may also occur in sports as a direct trauma. The sports injuries are seen with groin injuries and tears of the lower abdominal muscle in hockey, rugby, soccer, and any other type of sport that involves spinal rotation. 2

Clinical

The symptoms include burning or lancinating pain in the groin area. The pain occasionally may extend into the genitalia due to the significant overlap of the other cutaneous nerves. There is usually no loss of sensation.

On examination, there is pain and tenderness in the area of the scarring or entrapment. There may be hyperesthesia or hyposthesia in the area supplied by the nerve.

Three major criteria are used to diagnose the nerve. The first is a history of the injury. Pain can be elicited by palpating laterally near the scar injury area. Second, a definite area of hypoesthesia or hyperesthesia should be identified in the region of supply of the iliohypogastric nerve. Third, infiltration of a local anesthetic into the region where the iliohypogastric and ilioinguinal nerves depart the internal oblique muscle where symptoms can be reproduced on physical examination by palpation should provide relief. This could be enhanced by ultrasound guidance. If there is no relief with the injection, a different etiology should be sought to explore the problem. Differential diagnosis includes upper lumbar or lower thoracic nerve root pathology from a discogenic injury. No reliable EDX techniques are available to define the integrity of the nerve, although needle EMG of the lower abdominal musculature may suggest injury.

Treatment

Nonoperative treatments include ultrasound guided local injections of anesthetic and corticosteroid, oral medications, and physical therapy. Nonoperative treatment would include the neuropathic treatment model. If this is unsuccessful, surgical excision may be necessary.32

ilioinguinal neuropathy
Anatomy

The ilioinguinal nerve arises from T12 and L1 nerve roots. The nerve supplies the sensory branches that supply the pubic symphysis, the superior and medial aspect of the femoral triangle, the root of the penis and anterior scrotum in males, or the mons pubis and labia majora in females.
Ilioinguinal nerve injuries have been reported in hockey players. Clinical

The patients present with hyperesthesia or hypoesthesia. This injury is along the inguinal ligament and may radiate into the lower abdomen. Pain or tenderness may be present with application of pressure where the nerve exits the inguinal canal in up to 75% of the patients. Sensory impairment is common in this same distribution. Diagnosis is made by local infiltration of anesthetic and should provide relief within 10 minutes.

Treatment

Treatment is similar to that of the iliohypogastric nerve.

CONCLUSION

In conclusion, for an athlete to return to competitive sports, he or she must have the injured leg equal to 90% of the noninjured limb. The sooner the diagnosis has been made and treatment begins, the sooner the athlete can return to play. The athlete is very grateful when a difficult diagnosis is made and when appropriate treatment is provided. Removing the swelling from the nerve, allowing the nerve to heal, and finally exercising to allow the athlete to return to the sport of their choice. Through the use of a neurological examination and EDX testing, the neuromuscular physician is able to assist the athlete in the rehabilitation process.

REFERENCES

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Exercise in Neuromuscular Diseases

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Authors had nothing to disclose.

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**Exercise in Neuromuscular Diseases**

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**Objectives**

After attending this session, participants will be able to (1) review the effect of aging on muscle mitochondrial capacity and explore the link with sarcopenia, (2) assess the effects of physical activity and inactivity on skeletal muscle and cardiopulmonary exercise response in patients with metabolic myopathies, (3) understand the role of physical activity monitoring in a community environment to both measure and promote physical activity in persons with NMD, (4) review the effects chronic injury to the motor neuron and motor axon have on skeletal muscle function, (5) examine the role of electrodiagnostic studies in predicting response to exercise therapy, (6) evaluate the role of resistance exercise in acute and chronic diseases of the motor neuron and motor axon, as a countermeasure to sarcopenia at the molecular level, and as a rehabilitation modality in humans with muscle disease, (7) review the pertinent animal studies examining the effect of exercise on dystrophic muscle disease and the effect of exercise on humans with muscle disease, and (8) compare and contrast results seen in animal models versus human trials.

**Prerequisite**

This course is designed as an educational opportunity for physicians.

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Exercise in the Treatment of Aging Associated Sarcopenia and Metabolic Myopathy

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INTRODUCTION

Sarcopenia is a term describing the age-related loss of muscle mass to less than 2 standard deviations below age-matched normal subjects. It is usually measured as fat free mass (FFM) by whole body imaging methods such as dual energy x-ray absorptiometry. Sarcopenia has been reported in nearly 10% of people over age 70, and in 20% of those over age 80. The accompanying muscle weakness in sarcopenia leads to functional impairments in tasks that are important to personal independence, and can lead to a greater risk of falls. It has been estimated that the annual costs attributable to sarcopenia related impairments is approximately $18 billion (US dollars). Sarcopenia is clearly a multi-factorial process that involves apoptosis, motor unit (MU) loss, oxidative stress, alterations in protein turnover, inflammation, hormonal dysregulation, disuse, and mitochondrial dysfunction (Table 1). In addition to strength loss with aging, there is also a reduction in aerobic capacity. Although central factors such as cardiac output contribute significantly to the loss of aerobic capacity, there are a number of muscle-related factors that also contribute, especially a reduction in mitochondrial capacity.

Sarcopenia ultimately leads to a decrease in physical function and capacity. Falls occur in about 30% of people over the age of 65 who live independently. Nursing home residents who had a history of falls showed significantly lower dynamic strength measurements of the knees and ankles when compared to nonfallers. Leg muscle weakness results in a slowing of walking speed as well as a reduction in the ability to stair climb and rise from a chair. Finally, studies have shown an inverse relationship between leg strength and the prevalence of falls and fractures. Clearly countermeasures designed to increase strength and decrease the prevalence of sarcopenia should have a significant impact on society. Mitochondria and oxidative stress play an important role as modulators of age-associated sarcopenia.

Table 1 Molecular causes of sarcopenia

| • Physical inactivity   |
| • Oxidative stress     |
| • Mitochondrial dysfunction |
| • Apoptosis            |
| • Alpha motor neuron loss |
| • Reduced protein synthetic rate |
| • Accumulation of aging pigments including advanced glycosylation end products and lipofuscin |
| • Alterations in protein degradation (increased myofibrillar; decrease in other proteins) |

Additionally, exercise has the ability to provide a countermeasure for sarcopenia.

EFFECT OF AGING ON SKELETAL MUSCLE

Changes in Muscle Mass and Strength

A common characteristic of the aging process is a reduction in skeletal muscle mass and an infiltration of muscle with intramyocellular lipid and connective tissue. Cross-sectional studies have shown that FFM is maintained until about the sixth decade of life and then begins to decline. Several other studies have
found an age-associated loss of FFM. A progressive decline in strength is seen in association with lower muscle mass; for example, the isometric torque of the knee extensors (-44%) and elbow flexors (-32%) are both lower in a 69-year-old than in a 28-year-old man. Muscle power decreases even more rapidly with age than strength, and this reduction is also associated with impairments in physical function.

Several studies show that the age-associated decline in muscle strength is predominantly a function of the loss of skeletal muscle mass per se. For example, a 12-year longitudinal study of men from age 65 to 77 years found that the vast majority (90%) of the 20% to 30% strength loss (approximately 1.4% per year) was explained by the reduction in cross-sectional muscle area over the time period. Single-fiber experiments have shown that the amount of contractile proteins and the peak force normalized to muscle fiber size was not affected by aging. This finding implies that individual fiber "quality" is maintained with aging and that sarcopenia is a quantitative and not a qualitative process. In contrast, others have reported that there is an age-related decline in strength, independent of the muscle mass loss and have suggested that muscle quality also declines with age. At the whole muscle level, an increase in glycation-related collagen cross-linking in skeletal muscle from older adults, could also attenuate contractile force independent of muscle mass. An increase in other age-associated pigments, such as lipofuscin, is a characteristic feature of the aging process, but may not be linked directly with mitochondrial dysfunction. In addition to a reduction in muscle fiber size, there appear to be some changes in fiber type proportion that can also influence strength. The age-associated loss of muscle appears to affect type II fibers more than type I, with studies finding both smaller muscle fibers and myosin heavy chain IIa composition were smaller only in older women, but not men, as compared to younger adults. These observations suggest a general trend towards a decrease in whole muscle strength, through losses in type II fiber size and proportion. The cause of the loss of type II fibers is unclear; however, there are only about half the number of (MUs) remaining in the biceps brachii muscle of 60-to 80-year-old adults as compared to 20-to 40-year-old adults. A reduction in the number of MUs could explain the observation that the total number of type II muscle fibers in an entire muscle are reduced in older adults. Overall, the data implies that sarcopenia is associated with a reduction in the total number of muscle fibers, with a propensity for the type II fibers to be more affected.

Changes in Protein Turnover

At the protein level, sarcopenia is a consequence of an imbalance between the rates of muscle protein synthesis and muscle protein breakdown, with a negative net muscle protein balance. The rate of mixed muscle protein synthesis is lower in 60-to 70-year-old men and women as compared to 20-to 32-year-old adults. Similarly, the myofibrillar protein fractional synthetic rate was 30% lower in 60-to 70-year-old men, as compared to men less than 35 years of age, and the age-related reduction in muscle synthetic rate is associated with a reduction in myofibrillar protein messenger ribonucleic acid (mRNA) content (i.e., fast myosin isoforms). Importantly, knee extension strength and muscle mass were also positively correlated with myosin protein synthesis rates in older adults. The mitochondrial protein synthesis rates and electron transport chain activity show parallel declines with age, with no aging associated changes in the sarcoplasmic protein synthesis rates. Together, the data suggests that the synthetic rates of contractile and mitochondrial proteins are negatively affected by human aging and that these are linked to the functional deficits associated with aging.

Studies that have measured protein breakdown in older and younger adults did not indicate a difference in whole body proteolysis or urinary 3-methylhistidine excretion (an indirect measure of myofibrillar proteolysis). It has been reported that basal induced, but not acute exercise induced levels of 3-methylhistidine were higher in skeletal muscle microdialysate from older men as compared to younger men. In contrast, others have suggested that aging is associated with an accumulation of damaged, as evidenced by an increase in the half-life of proteins and a lower ubiquitin-proteasome activity. Proteomic studies in rat skeletal muscle have shown lower overall abundance of proteins such as creatine kinase, myosin light chain-3, and troponymosin; and higher levels of myosin light chain-1, aconitase, and adenylate kinase. The apparent conflicting myosin light chain results from the latter study, show that the crude measurements of synthesis and breakdown do not give the complete picture of the specific proteins that are altered by sarcopenia.

Mitochondrial Dysfunction and the Link With Sarcopenia and Apoptosis

Several studies have demonstrated a reduction in mitochondrial enzyme activity with aging. The cause of the age-related decrease in mitochondrial capacity is unclear; however, studies have shown that there is a coordinate down-regulation of genes involved in mitochondrial function in skeletal muscle from older adults. Using a targeted quantitative real time polymerase chain reaction approach, robust evidence for mitochondrial dysfunction in skeletal muscle from older versus younger adults was found (Figure 1). In addition, there has been a discovery of an age-associated accumulation of mitochondrial deoxyribonucleic acid (mtDNA) deletions in human skeletal muscle. Animal studies suggest that the accumulation of mtDNA deletions with aging is highest in the type I fibers (with higher mitochondrial volume). Given the few introns and lack of protective histones in mtDNA versus nuclear deoxyribonucleic acid (DNA), there is a higher propensity for the stochastic accumulation of oxidative damage mediated DNA mutations in mtDNA as compared to nuclear DNA. Although somewhat controversial, it has been suggested that the progressive accumulation of mtDNA mutations is thought to occur as a result of a "vicious cycle," whereby ETC generated free radicals further induce mtDNA...
mRNA abundance for selected genes involved in antioxidant defenses, apoptosis, and mitochondrial structure/function in vastus lateralis from young (20 to 26 years) n=12) and older (65 to 79 years) n=12) adults.

COX IV = cytochrome c oxidase sub-unit IV; mfn2 = mitofusin 2; MRNA=messenger ribonucleic acid; SOD1 = Copper zinc-super-oxide dismutase; SOD2 = magnesium-super-oxide dismutase;

Some have suggested that part of the sarcopenia process is related to apoptosis of myonuclei and a subsequent loss of the myonuclear domain under control of the lost nuclei. The mitochondria also play an important role in the activation of apoptosis through the release of cytochrome c, which interacts with Apaf-1 and caspase-9 to form the apoptosome, which activates downstream effector caspsases, such as caspase-3. Activation of apoptosis by the mitochondrial pathway appears to involve an opening of the mitochondrial permeability transition, which in turn is opened by free radicals (predominantly peroxynitrate). The abundance of a number of transcripts for apoptosis factors including caspases-3, -8, and -9 and apoptosis inducing factor were higher in skeletal muscle of older rats and mice also show evidence of a p53 associated activation of apoptotic pathways. Finally, the mitochondrial mutator mouse has a large increase in mtDNA deletions and point mutations. This is caused by a defective polymerase gamma mutation and displays an aging phenotype which is associated with an increase in cleaved caspase-3 in skeletal muscle. Although definite evidence for apoptosis in human sarcopenia is still somewhat circumstantial, it is well supported in the animal-based literature. It is important to note that a loss of only 0.5% of the myonuclei from age 30 to 70 years could account for a 20% decline in muscle mass, and yet such a low level of myonuclei undergoing apoptosis at any given point in time would be difficult to detect with current in situ methods such as terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick end labeling staining.

**AGING AND RESISTANCE EXERCISE (EFFECTS ON MUSCLE MASS AND FUNCTION)**

Several groups have reported that resistance (RES) exercise training induces muscle hypertrophy and increases the rate of muscle protein synthesis in middle aged, elderly, and physically frail adults. For example, 12 weeks of whole body RES exercise resulted in an increase in type II muscle fiber area in 64-to 86-year-old women and 65-to 72-year-old men. Increases have been found in both type I and IIX muscle fiber areas following 4 months of RES training in older men and women. A 2-year longitudinal trial of RES exercise training reported increased leg press (32%) and military press (90%) one-repetition concentric maximum (1 RM), and knee extensor muscle cross-sectional area (9%) in 60 to 80 year old men and women. Long-term exercise also appears to be protective against age-associated strength loss for Master’s athletes (69 ± 1 year), who performed...
RES exercise training and had muscle strength that was similar, and in some movements, higher than young, sedentary men. An increase in strength after RES exercise as well as robust improvements in strength following 4 and 7 months of RES exercise training are consistent findings.

Studies have suggested that the increase in strength following RES training in older adults was largely due to neural adaptations, given that muscle hypertrophy was less than expected for the magnitude of the strength improvement. A 2-year longitudinal RES training study in older men and women found that the increase in leg press (32%) and military press (90%) strength was much greater than the corresponding increase in the cross-sectional thigh area which increased by only 9%. Part of the neural adaptation could be due to the fact that the neuromuscular junction undergoes degeneration with hypodynamia and aging, and neural adaptations always precede muscle hypertrophy in response to RES training. Another factor that may explain an RES training increase in strength with only a minimal to modest increase in muscle mass would be an increase in muscle quality, as measured with functional testing in 65-to 75-year-old men. At the single-fiber level, there appears to be an increase in muscle fiber area, strength, and contractile strength and power for men, with no effect of RES training in women. One study found that the minimal increase in strength and size of single fibers following RES training in older men (80 to 86 years) was minimal in comparison to the increase in whole muscle strength. The authors concluded that an increase in neural activation was the likely explanation.

The functional benefits of RES exercise training have been evaluated in a large-scale trial of 72-to 98-year-old physically frail nursing home residents. The RES exercise training increased muscle strength (113%), gait velocity (12%), stair climbing power (28%), spontaneous physical activity, and thigh muscle cross-sectional area (2.7%). There have also been findings of consistent improvements in functional capacity in older adults following both a 4 and 6 month supervised RES exercise program. An increase in muscle function can have significant beneficial effects on activities of daily living (ADL) and may have a significant long-term beneficial impact upon health care costs by reducing the burden of illness associated with weakness and immobility. Following 6 months of RES training, improvements in strength and functional capacity in older adults has been seen, (Figure 3).

The data suggests that some of the possible aerobic benefits of RES training in older adults may be due to a direct effect on mitochondrial function at the level of the skeletal muscle. Recently it has been found that 4 months of RES training is associated with an increase in COX enzyme activity as well as citrate synthase total protein content in older adults. Furthermore, 6 months of RES exercise training reduced mtDNA deletions in skeletal muscle from older men and women (Figure 4A), and “reversed” the transcriptome signature of aging at the skeletal muscle level. RES exercise training has been shown to be associated with a reduction in whole body and muscle markers of oxidative stress, and an increase in antioxidant defense enzymes such as manganese superoxide dismutase. More recently, it has been discovered that

RES = resistance exercise training
6 months of RES training also reduces a marker of DNA damage in skeletal muscle (8-hydroxy-2-deoxy-guanosine) (Figure 4B).

One potential source of the improvements in mitochondrial function and anti-oxidant defenses following RES training could be the recruitment of the satellite cells which can fuse with the mature muscle and “dilute” the older dysfunctional mitochondria. Some but not all studies have shown that the total number of satellite cells are lower in older adult muscle, yet they retain the full ability to activate and regenerate damaged muscle; however, other studies have shown several properties of aged satellite cells are altered, including antioxidant defenses. Following an acute bout of eccentrically biased RES exercise, there is an increase in the number of activated satellite cells in older adults, however, it was only one third of that found in younger adults. Recent data shows that mtDNA deletions and reduced mitochondrial enzyme activity were not present in myoblast cultures derived from older versus younger adults (myoblasts are derived from the satellite cells) (Safdar, A., and colleagues, manuscript in preparation, 2008). In combination, these data suggest that RES training in older adults is associated with an activation and recruitment of the satellite cells into the mature muscle in older adults, which represents a form of mtDNA gene shifting. This phenomenon may occur because satellite cells remain quiescent and relatively undamaged from lifelong exposure to free radicals derived from mitochondrial respiration. They become activated and fuse only after responding to signals for muscle growth or repair of muscle damage.

**AGING AND ENDURANCE EXERCISE (EFFECTS ON MITOCHONDRIA AND FUNCTION)**

At the whole body level, several longitudinal studies have found that the maximum rate of oxygen consumption (VO\(_2\)max) increases following endurance (END) exercise training in older adults. At the skeletal muscle level, this is associated with an increase in capillarization, mitochondrial function, and an increase in myosin heavy chain I mRNA and protein content. Studies have also found that END exercise training increased intramyocellular lipid content, whole body aerobic capacity, and mitochondrial enzyme capacity in older adults. Cross-sectional studies have found that Masters END athletes did not show the expected age-related decline in mitochondrial function, and Master’s athletes show about 50% of the decline in aerobic capacity as compared to sedentary individuals. There is also a significant decline in insulin sensitivity with aging, which can be significantly improved following END exercise training. In addition, END exercise training has been associated with a reduction in both abdominal fat and dyslipidemia. Furthermore, in older adults, reductions in blood pressure are more consistently observed following END exercise training as compared with RES exercise training. END exercise does not usually lead to an increase in muscle mass; however, given the robust benefits of END training on enhancing the mitochondrial capacity, it is tempting to speculate that END training may attenuate the progression towards sarcopenia.

**CONCLUSION**

Aging is associated with a reduction in skeletal muscle mass and function that can lead to limitations in ADLs. A reduction in functional capacity can lead to an increase in healthcare costs due to an increased reliance upon institutionalized living and the costs associated with falls (i.e., hospitalization for fractures and other injuries). The aging process is multifactorial and eventually leads to an increase in markers of oxidative stress and mitochondrial dysfunction. Whether or not mitochondrial dysfunction and oxidative stress are directly linked, as suggested by the original mitochondrial theory of aging, is still controversial; however, they both improve following RES and END exercise. There is no question that RES exercise can lead to improvements in muscle function in older adults. This is likely due to both intrinsic improvements in muscle structure and function as well as an enhancement of neural activation. END exercise is associated with improvements in aerobic capacity and mitochondrial function, with benefits also seen in cardiovascular risk factors. Unlike RES exercise training, where there is a “spill over” effect of benefits in the classical adaptations due to END exercise (i.e., increased mitochondrial capacity), there has been little work examining whether END exercise training leads to an increase in strength. It is quite likely that a combination of both END and RES exercise training will lead to the optimal benefit for older adults, but experimental evidence is currently lacking.

The benefits of exercise training in older adults may extend far beyond the observations of higher muscle mass and strength and mitochondrial capacity. For example, a Cochrane review listed “muscle strengthening” as the first intervention associated with a reduction in falls in older adults (3 trials, n = 566, relative risk = 0.80), due in part to an improvement in balance. In addition to the benefits of RES exercise training as a countermeasure to sarcopenia, several studies in animals and humans have found that habitual physical activity can also increase longevity. A recent study has discovered that higher levels of physical activity are more important than body fat as a predictor of all cause related mortality. In most developed countries, the proportion of the population over the age of 65 years is expected to grow over the next few decades. It will therefore be important to evaluate and implement optimal exercise programs.

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INTRODUCTION

Exercise intolerance is an important clinical manifestation of impaired skeletal muscle metabolism, where in addition to the underlying disease process, secondary effects of deconditioning and physical inactivity contribute to its progressive worsening. Exercise intolerance may be clinically defined by dyspnea, tachycardia, weakness, or a perception of fatigue in active muscle, all of which present during minimal to moderate levels of physical exertion. It is well known that exercise training reverses the effects of deconditioning in healthy individuals and is being used to improve exercise tolerance in a variety of chronic conditions (e.g., cardiopulmonary disease). However, until recently, the effects of exercise training in metabolic myopathies have not been well-studied, due in part to the heterogeneous nature of these disorders and the unfamiliarity of the field of exercise physiology within the context of neuromuscular medicine. Although the application, safety, and efficacy of exercise training remain to be firmly established in adult patients with metabolic myopathies, the current understanding in the field as it relates to two disorders representing glycolytic and mitochondrial metabolic pathways will be reviewed. These disorders are myophosphorylase deficiency (MD also known also as McArdle’s disease) and mitochondrial myopathies, attributable to defects of the electron transport chain (ETC).

ADAPTATIONS TO EXERCISE TRAINING AND DETERTRAINING

Exercise training can involve either endurance activity, resistance activity, or a combination of the two. Endurance is generally defined as aerobic activity that involves the use of large muscle groups for sufficient intensity and duration (30 minutes, 50% to 85% of peak rate of oxygen [O₂] utilization or the maximum amount of O₂ consumed while exercising [VO₂max]). Resistance activity typically involves a demand of low volume, highly intense contractions of muscle fibers of approximately 50% to 75% of one maximal repetition. Physiological and phenotypic adaptations to the regular performance of the two modes are generally different.

Endurance Training

Endurance training (ET) or aerobic training induces adaptations in the heart, peripheral circulation, and skeletal muscle systems that increase both maximal and submaximal exercise capacity by enhancing the delivery of O₂ to the exercising muscle and increasing muscle capacity for O₂ utilization through oxidative metabolism. Greater O₂ delivery is achieved through increases in cardiac output (due to increases in stroke volume rather than maximal heart rate), whereas greater utilization of available O₂ by trained skeletal muscle (resulting in a greater arteriovenous O₂ difference) is attributable to increases in capillary density, vascular conductance, and mitochondrial oxidative capacity. These peripheral adaptive responses are localized and evident only in trained muscles. A key feature of enhanced muscle oxidative capacity is increased mitochondrial biogenesis, which is associated with increases in respiratory chain enzyme levels that lead to an increased capacity to generate energy via oxidative phosphorylation. In healthy individuals, this adaptation in metabolic efficiency is thought to play a major role in the ability to perform submaximal work with less effort and for longer duration. This can be evidenced by lower blood lactate levels and heart rates than those of untrained individuals at the same absolute level of submaximal exercise. Furthermore, increases in maximal exercise capacity VO₂max are limited by improvements in O₂ delivery (cardiac output).

Mitochondrial biogenesis is a notably complex process owing to the fact that the formation of mitochondria are under dual genomic control with the majority of genes encoded in the cellular nucleus and a subset of genes (22 transfer ribonucleic acid [tRNA], 2 ribosomal RNA, and 13 polypeptides) encoded by copies of mitochon-
drial deoxyribonucleic acid (mtDNA) within the mitochondrial matrix. The mitochondrial genome is highly dynamic, with frequent mutations and recombination events. Endurance exercise-specific muscle contractions signal a cascade leading to the coordinated increase in the rate of transcription of nuclear-encoded genes, as well as mtDNA replication, and copy number that support the increased rate of synthesis of mitochondrial-encoded genes. The gene products from both genomes must then be combined to form a functional electron transport chain with the help of an increasing number of identified assembly factors.

**Resistance Training**

Resistance training (RT) normally induces physiological adaptations that differ from those of ET. The lifting of heavy weights to overload skeletal muscle during concentric (muscle shortening) or eccentric (muscle lengthening) contractions leads primarily to increases in strength, power, and local muscle endurance. Both neural and muscular factors modify the expression of human strength, however, as evidenced from surface electrode electromyography, enhanced neural facilitation (increased motor unit recruitment and efficiency) predominates in the earlier phases of training. Beyond the first few weeks, muscle hypertrophy occurs as a result of the synthesis and accretion of contractile proteins, myosin and actin. This occurs both within the whole muscle and in the individual myofibrils through the addition of intracellular myofibrils. Essential to the process of hypertrophy is the activation of satellite cells, mononuclear, and myogenic progenitor cells that typically exist in a state of relative mitotic quiescence under the basal lamina of mature myofibers. In response to stimuli such as overload or trauma, satellite cells become activated, and proliferate daughter cells to either fuse to the existing fiber or participate in fiber regeneration. The fusion of satellite cell contents provides additional nuclei to the existing fiber, leading to synthesis of additional contractile proteins and maintaining the nuclear cytoplasmic ratio.

**Deconditioning**

These previously mentioned physiological and metabolic changes that are responsible for improved exercise capacity are not permanent but are reversible upon cessation or marked reduction of an exercise training stimulus. This leads to partial or complete reversal of training-induced adaptations throughout the cardiopulmonary and skeletal muscle systems that decrease maximal and submaximal exercise performance. Notably, detraining leads to decreases in maximal cardiac output, muscle capillary density, mitochondrial volume, and oxidative enzymes, as well as a loss of neural adaptations and muscle contractile proteins.

**MITOCHONDRIAL MYOPATHIES**

Mitochondrial myopathies constitute a heterogeneous group of metabolic disorders in terms of clinical presentation that range from single organ (affecting visual and auditory pathways, gastric and endocrine systems, central nervous system, myopathy, or cardiomyopathy) to multi-system involvement. Brain and skeletal muscles are particularly susceptible to mitochondrial dysfunction due to their high requirements for oxidative energy metabolism. Skeletal muscle is almost invariably affected in adult patients, and while myalgias often involve fixed weakness and recurrent myoglobinuria, exercise intolerance is a more common manifestation of the underlying defect in oxidative phosphorylation with severity that can range from mild to disabling. The underlying molecular defect involves either a mutation in nuclear or mtDNA, both of which ultimately impair electron transport and oxidative phosphorylation. While the combined prevalence of these defects is estimated to be 1 in 5000, the diagnosis is complicated by molecular and phenotypic heterogeneity, as well as by other unique features of mitochondrial genetics. The majority of known mutations are in mtDNA, with over 200 mutations identified in the 16.5 Kb circular molecule to date. Depending on the location of the mutation within the genome as well as the type (deletion or point mutation), a single complex or multiple complexes (those containing mtDNA encoded subunits; complex I, III, IV, and V) of the ETC may be affected. Furthermore, mutations in mtDNA coexist with wild-type mtDNA molecules within the cell in a condition known as heteroplasmy. The level of mutation can vary, but once it exceeds a certain critical threshold, phenotypic expression of the mutation occurs and is evidenced by cellular oxidative impairment. These oxidatively deficient myofibers are distributed variably throughout the muscle, intermixed with myofibers that contain a normal capacity for oxidative phosphorylation and predominantly wild-type mtDNA (or subthreshold levels of mutant mtDNA).

In addition to mtDNA defects, mutations in nuclear genes are an important and growing cause of mitochondrial myopathy. Nuclear genes encode for the majority of mitochondrial proteins (approximately 1500), however, only about half of these have been identified, which contributes to difficulties in diagnosis. Mutations in nuclear DNA are involved in impairing electron transport chain function as they either encode for a complex subunit directly, encode ancillary proteins needed for complex assembly, or encode genes that affect intergenic signaling which affects the abundance and quality of mtDNA. While the classification and molecular effects of nuclear mutations in mitochondrial disease is complex and can be reviewed in other sources, in adult muscle, these mutations are generally associated with residual activity of affected enzymes and the condition of mitochondrial heteroplasmy does not exist.

**Rationale for ET**

Based on the normal adaptive processes within skeletal muscle, the rationale for ET in patients with mitochondrial myopathies is evident: to induce mitochondrial biogenesis, thereby stimulating increases in numbers of functional mitochondria and capacity for oxidative phosphorylation. This rationale is important as it addresses both the disease process as well as the maladaptive effects of deconditioning. Habitual inactivity and sedentary lifestyles have been postulated to lead to a down-regulation of muscle mitochon-
have assessed ET effects on mutation load in a group of patients with a homogenous mutation in mtDNA (single large-scale deletion) and a group with more varied mtDNA mutations. In both studies, significant increases in physiological and biochemical markers of mitochondrial function were detected without any changes in level of mutant mtDNA and breathing capacity following the cessation of training, confirming the maladaptive effects of detraining. Studies are currently ongoing to determine the effects of mitochondrial biogenesis within single myofibers and on absolute levels of wild-type mtDNA, which may ultimately dictate improvements in cellular oxidative capacity in response to the ET stimulus. Evidence supporting increases in wild-type mtDNA despite changes in mutant mtDNA are needed to safely prescribe ET as a therapeutic approach for patients with mitochondrial myopathy. To summarize, the effects of ET on the mutant mtDNA proportions within muscle have not been firmly established and out of the seven published reports (Table 1) no adverse effects (other than the cellular increase in mutant mtDNA) have been reported.

**Rationale for RT**

While fixed weakness attributable to the underlying genetic defect may present in patients with mitochondrial myopathy, general physical inactivity contributes more prominently to a reduction in overall muscle strength. Although RT may be expected to reverse this loss, studies that address this directly in patients with nuclear or mtDNA mutations are scant. Cejudo and colleagues incorporated moderate-intensity upper body strength training into an overall exercise training program which included ET and reported marked improvements in muscle strength and endurance with no adverse effects.

More intriguingly however, is that although RT does not normally induce mitochondrial biogenesis in healthy, younger individuals, a unique and alternate rationale has focused on using RT to improve the actual disease process in a subgroup of patients with sporadic mutations of mtDNA (nonmaternally inherited mutations). Dramatic tissue variation in mitochondrial heteroplasmy has been found to exist in these patients, where despite high abundance in mature skeletal muscle, levels of the causative mutation are low or undetectable in satellite cells. The idea of gene-shifting (fusion of satellite cells devoid of mutant mtDNA) was proposed through two case studies where experimentally induced muscle necrosis (biopsy trauma and toxin injection) was followed by myofiber regeneration containing lower mutation levels. Because RT is known to serve as a stimulus for satellite cell induction within active skeletal muscle and offers a more feasible, physiological approach, it was hypothesized that RT would lead to shifting of normal mitochondrial genes from satellite cells to mature muscle, lowering the level of mutation below threshold and improving muscle oxidative capacity. The first case study showed a significant decrease in mutant mtDNA levels following short-term, high-intensity strength training in the arm, however, markers of muscle strength and oxidative capacity were not assessed. A recent study involving 12 weeks of progressive overload leg RT...
in a group of eight patients with single large-scale deletions demonstrated significant increases in muscle strength, despite myofibre damaged and regeneration, and improvement in muscle oxidative capacity along with increases in the proportion of neural cell adhesion molecule positive satellite cells. Together, these findings support the notion of RT-induced mitochondrial gene-shifting in muscle containing satellite cells which have low or absent levels of deleted mtDNA. Further studies are aimed at refining parameters of the exercise training protocol in order to maximize the training effect on wild-type mtDNA levels and promote RT as a potential treatment approach.

### Myophosphorylase Deficiency

Myophosphorylase Deficiency, also known as McArdle’s disease or glycogen storage disease type V, is the most common inborn error of muscle carbohydrate metabolism and one of the most common causes of recurrent myoglobinuria.\(^8\) Mutations in the myophosphorylase gene typically lead to complete loss of enzymatic activity. As such, there is a block in muscle glycogen breakdown resulting in severe limitation in both anaerobic metabolism as well as aerobic metabolism due to the fact that MD limits substrate availability as muscle glycogen is required for peak rates of oxidative phosphorylation.\(^8\) Without glycogen, the capacity for aerobic exercise is reduced and is greatly dependent on an availability of bloodborne fuels (glucose and free fatty acids). In addition to exercise intolerance, more strenuous muscle activities (which normally engage anaerobic glycolysis rather than oxidative phosphorylation) often trigger muscle contractures, rhabdomyolysis, and myoglobinuria \(^9\), leading to potentially severe consequences. In general, the avoidance of exercise has been recommended to patients with MD. As previously mentioned, the adoption of a sedentary lifestyle can be expected to further limit exercise tolerance by decreasing circulatory and muscle metabolic capacity. In this case, the delivery of bloodborne fuels that are essential for oxidative metabolism when glycogen breakdown is blocked would be limited, as well as utilization or metabolism of fuels within mitochondria.

ET’s potential benefit to patients with MD has only recently been assessed. As part of a study, eight patients underwent 14 weeks of cycle training at 60% to 70% of maximal heart rate.\(^9\) The patients all completed the training program without symptoms of muscle pain or cramping. As indicated by blood creatine kinase levels before and after individual training rides, exercise within the prescribed guidelines did not provoke muscle injury. Significant improvements were detected in peak work, oxidative capacity, cardiac output during initial exercise, as well as after the spontaneous second wind, which is the characteristic increase in oxidative capacity that occurs after the first 8 to 10 minutes of sustained aerobic activity attributable to arrival and increased oxidation of bloodborne fuels in muscle. Furthermore, increased muscle mitochondrial volume was detected in response to the training. Therefore, although exercise training can not augment activity of the missing myophosphorylase, the authors concluded that ET-induced adaptations increase the capacity to deliver bloodborne fuels to working muscle as well as the range of oxidative capacity within muscle.\(^9\) This raises the threshold at which dynamic exercise could pose a risk for muscle injury while also supporting the safety and efficacy of regular submaximal (an intensity which is fuelled by oxidative metabolism) exercise as a component of therapy for MD, provided that the patients exercise within specified heart rate guidelines.

Due to the susceptibility of skeletal muscle to contractures, rhabdomyolysis, and myoglobinuria, MD patients must be advised not to engage in ischemic, isometric, and maximal effort dynamic exercises. These types of activities normally engage anaerobic glycolysis which are known to trigger injury.\(^9\) Therefore, although the precise conditions of injury-provoking exercise need to be more clearly defined, RT is not recommended for MD patients.
REFERENCES


INTRODUCTION

The role of exercise in disorders affecting the motor neuron (MN) and motor axon will be examined. The hallmark of many of these disorders is progressive muscle atrophy and weakness, which leads to substantial impairment and disability. Many diseases affecting the MNs or axons are slowly progressive, with weakness that advances over the course of many years (e.g., Charcot-Marie-Tooth disease [CMT]). Others are much more rapidly progressive (e.g., amyotrophic lateral sclerosis [ALS]), while still others may present with long periods of relative stability followed by more rapid or stepwise progression (e.g., post-polio syndrome [PPS]).

Great strides have been made in recent years with regard to understanding the biological processes of these various diseases. However, to date, no curative treatments exist, and the few available pharmacological therapies (e.g., riluzole for ALS) only minimally alter the course of disease progression. Therefore, rehabilitation interventions are at the center of caring for individuals with these disorders. Exercise, particularly resistance training, may be useful to increase or maintain muscle mass and strength and help maintain the highest levels of ability and function in these patients. Resistance exercise plays an important rehabilitative role in disorders of the MN and motor axon. The following will focus primarily on the role of resistance exercise in CMT, ALS, and PPS.

General Considerations

The majority of the progressive diseases of the peripheral motor system result in weakness stemming from skeletal muscle atrophy. In turn, muscle weakness is the primary cause of disability in patients suffering from these disorders. Lower extremity (LE) weakness and limited functional mobility are often the most concerning problem for these patients.15 Although the cause of atrophy and weakness varies, based on the specific disorder, some general observations regarding the underlying pathophysiology can be made. The primary mechanism in most cases is degeneration, or loss of MNs or motor axons with associated denervation of muscle.18 Even in the most rapidly progressive disorders, collateral reinnervation may result in some compensation, but this is eventually unable to keep up with the extent of MN or motor axon loss and as a result, atrophy and weakness occur.4 However, factors other than progressive denervation that contribute to weakness may include: reduced or inadequate central drive to the lower MN, upper MN involvement in ALS, atrophy of the still existing muscle fibers, possible neuromuscular transmission failure or distal conduction block in immature reinnervated motor units (MUs), fatigue that is secondary to deconditioning (both cardiovascular and peripheral), and non-neurologic factors such as joint contracture, altered joint biomechanics, and instability.15,24,25 Obviously, resistance exercise can ameliorate only some of the factors that lead to weakness, and in some cases there may be deleterious effects.

Charcot-Marie-Tooth Disease

CMT or the hereditary motor sensory neuropathies encompass a family of inherited peripheral neuropathies that present with slowly progressive, distal to proximal muscle atrophy, and weakness.17,27 The genetic defect in CMT1A, which is involved in the most common form of CMT (70% of cases), is caused by either a duplication, or less commonly, a point mutation in the PMP22 gene, resulting in functionally abnormal compact myelin in the peripheral nervous system. CMT1A is characterized by markedly slowed conduction velocities in motor and sensory nerves (often 15–20 m/s), areflexia, and the occurrence of progressive motor and sensory deficits by the mid-teens in most cases. CMT-X presents with similar clinical features but with inter-
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mediate nerve conduction slowing. Alternatively, CMTII encompasses a number of disorders where the primary pathology is within the axon, as opposed to the myelin (e.g., mutation in Mitofusin2 for CMT 2A2). However, regardless of whether the primary pathology is within the myelin or axon, the eventual disability is secondary to progressive axonal loss that results in motor and sensory deficits. Other causes of weakness, such as disuse atrophy and deconditioning, may compound the situation. To date, there are no effective pharmacologic therapies for the inherited neuropa-thies. Therefore, rehabilitation interventions, including resistance exercise, are the mainstay of treatment.

A number of studies have examined the role of resistance exercise in patients with slowly progressive neuromuscular disorders. In some of these studies, patients with CMT have been included. These studies, in general, have suffered from a number of shortcomings. For example, in most studies patients with a number of different disorders were combined (e.g., patients with muscular dystrophy [MD] and CMT were in the treatment group). All too often, inadequate sample sizes were used and the studies were likely underpowered. Additionally, most studies suffer from the absence of non-exercising controls and in most cases, no functional outcome measures were used. Lindeman and colleagues carried out the most methodologically sound and comprehensive study of resistance exercise in patients with CMT. The study also included a group with myotonic dystrophy, but the groups were analyzed separately. Subject assignment to either a training or control group was performed randomly and the subjects were matched based on baseline strength. The training group performed knee extension and flexion exercises, as well as hip abduction exercises with weights strapped to the limb 3 times per week for 24 weeks. The primary outcomes were isokinetic knee extension and flexion torque, as well as functional outcomes (e.g., timed motor tasks, timed ascending and descending stairs). The myotonic dystrophy group showed no improvement in torque or function, whereas the CMT group demonstrated improved torque, but not improved function. There was no evidence of muscle damage, as measured by serum myoglobin levels. Lindeman and colleagues later reported that the maximum surface electromyography (EMG) signal increased substantially during the first 8 weeks of training, suggesting that the increased strength observed in this time period was related to neural factors (improved central drive) and that the subsequent smaller gains were likely related to muscle hypertrophy. More recently, Chetlin and colleagues examined the potential benefit of combining strength training with creatine supplementation in patients with CMT. Twenty patients were randomized into two groups that would either perform resistance training alone, or would perform the training and take 5 gm/day of creatine supplementation. While there were no differences between the creatine and training groups, the combined analysis revealed an increased Type I fiber diameter, increased strength, and improved activities of daily living (ADLs) on timed functional tasks. Thus, there was evidence of strength gains and muscle hypertrophy, but no further added benefit from creatine supplementation was found. Overall, there is reasonable evidence that progressive resistance exercise can improve strength and possibly function in patients with mild to moderately severe CMT, at least for larger proximal muscles. The question remains as to whether or not resistance exercise could improve strength and function in the more severely affected distal muscles given the underlying pathophysiology.

Post-Polio Syndrome

Paralytic poliomyelitis, an infectious disease of the anterior horn cell, has been eliminated in the Western world as a result of effective vaccination programs, and its worldwide incidence has dramatically decreased. However, over the past 20 years, there has been increasing acceptance and recognition of the development of new motor deterioration in those previously affected by paralytic polio, following long periods (often decades) of relative neurological stability. In addition to new motor deficits, many patients with the so-called PPS experience neuromuscular fatigue, central fatigue, and pain. It has been reported that as many as 60% of those affected by prior polio may develop new weakness. A survey conducted in 1987 showed that because there were more than 600,000 people in the United States with prior polio, PPS may become the most common MN disorder.

A full review of the pathophysiology of PPS is beyond the scope of this manuscript. There are two leading hypotheses to explain the new motor deficits in PPS. The first suggests that there is progressive deterioration of the distal motor axons in the greatly enlarged MUs. This is supported by single-fiber EMG (SFEMG) observations as well as data from muscle biopsies. The other leading hypothesis suggests that loss of entire MUs leads to the new onset weakness. Aging, in and of itself, is associated with significant MU losses, the impact of which is substantially greater, as those with prior polio have less and larger MUs. This “accelerated aging” hypothesis is based largely on electrophysiological data wherein MU estimation techniques have shown reductions in MU numbers in longitudinal studies. Other contributing factors to weakness include disuse, pain inhibition, overuse of severely affected muscle groups, and immunological mechanisms.
increase of 61% was reported in the weight lifted, but there was no significant improvement in isokinetic or isometric peak torque of the knee extensors. Creatine kinase values did not change over the course of the program and perhaps most importantly, there was no evidence of increased jitter, blocking on SFEMG, or change in the macro EMG amplitudes to indicate any further injury or deterioration to the enlarged MUs. Chan and colleagues extended these findings and examined the impact of 12 weeks of isometric training of the thenar muscles in five subjects with clinical and EDX features of PPS as compared to a non-exercising PPS control group. These subjects were comprehensively examined at baseline with MU number estimates, maximal voluntary and evoked force measures, and twitch interpolation to assess adequacy of central drive. They reported significant improvements in strength in the PPS training group that were largely explained by increased central drive. There was no indication of further MU loss as a result of the training. Therefore, strength training appears to be safe and potentially beneficial for muscle groups with at least moderate weakness in patients with PPS. To date, no studies have demonstrated functional improvement. This would likely require much larger sample sizes and longer durations of training.

**Amyotrophic Lateral Sclerosis**

ALS is a progressive, ultimately fatal, disorder of the upper and lower MNs. ALS often presents with focal weakness limited to one limb but eventually spreads to other segments of that limb and becomes generalized. The hallmarks of ALS are muscle atrophy and weakness from lower MN loss and weakness, as well as fatigue and spasticity from upper MN involvement. The overall incidence ranges between 0.4 to 2.4 cases per 100,000, which will likely increase as the population ages. Currently, the only pharmacologic treatment that has been shown to prolong life is riluzole. Therefore, there is considerable interest in exploring other potential therapeutic interventions that may improve strength and ultimately improve function, or at least ameliorate the rate of decline.

Traditionally, due to the progressive nature of ALS, exercise was believed to be deleterious. It has been postulated that severely weak muscles are more susceptible to overuse injury as they are already functioning at levels close to maximal voluntary contraction when simply performing ADLs. Therefore, some experts have recommended that patients with ALS do no exercise beyond that required for day-to-day activities.

Recent studies using animal models of MN disease have provided some evidence that endurance exercise slows disease progression. It has been reported that treadmill running 5 days per week at 13 m/min led to a significant increase in the life span of G93A-SOD1 male, but not in female mice. Alternatively, another study found that treadmill running at 16 m/min delayed disease onset and prolonged survival in transgenic low-copy hSOD1 female mice, whereas there was no effect in males. The most pronounced effects of exercise using the SOD1 mouse model were reported in an adjunct study by Kaspar and colleagues. Mice that were exposed to an exercise wheel 6 hours per day, beginning in the pre-symptomatic state, survived 33% longer than those not exposed to the exercise. Alternatively, high intensity treadmill running at 22 m/min did not delay disease onset in G93A-SOD1 male and female mice, and was found to shorten lifespan in the males. There is evidence from these animal studies that low to moderate intensity exercise may be of benefit, whereas, high intensity endurance exercise may be detrimental.

There have been very few controlled studies that have examined the potential benefit of resistance exercise in patients with ALS. Traditional thinking cautioned against therapeutic exercise due to concerns of overuse of denervated or severely weak muscles. However, early case reports provided generally positive results that have led to at least two controlled studies.

Drory and colleagues examined the potential benefit of a twice daily, home based exercise program consisting of an individualized program of modest intensity exercise designed to improve endurance in comparison to a usual activities control group. They reported less deterioration on the ALS Functional Rating Scale (FRS) and Ashworth spasticity scale at 3 months, but no difference at 6 months. There were too few subjects remaining at 9 and 12 months for analysis. The most rigorous examination of resistance exercise in ALS patients to date involved 27 patients with clinically definite or probable ALS that were randomized to a daily stretching and resistance exercise group, or control group that performed daily stretching. Of the 27 patients, only 8 patients in the resistance exercise group and 10 patients in the control group completed the study. Despite the drop-out rates, at 6 months, the resistance exercise group had significantly higher ALS-FRS scores, SF-36 physical function subscale scores, and less decline in leg strength. No deleterious effects were reported. Therefore, there is some support for resistance exercise to be used as a potential intervention to slow disease progression and maintain higher levels of function in patients with ALS. However, larger studies are required to provide more definitive evidence and to further examine the optimal exercise modes, intensities, and overall volumes.

**CONCLUSION**

In summary, there is considerable support for the prescription of resistance exercise in disorders of the MU and axon. There is little evidence that light to moderate exercise is detrimental in muscle groups with at least grade 3 or better strength. However, much remains to be learned in terms of optimizing resistance training programs for these patient populations. Ideally, future studies will require homogeneous patient populations, adequate sample sizes, training durations of 6 months or greater, and functional outcome measures.

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Physiological Adaptations and Responses to Exercise Training in Neuromuscular Disease

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BACKGROUND

It is well established in both humans and animals that exercise causes muscle injury and that eccentric exercise has a more damaging effect than concentric exercise.4,21,22,23,47,49,59 In humans with neuromuscular disease (NMD), there has been considerable controversy regarding the use of exercise, particularly high intensity strengthening programs.4,21,22,23,47,49,59 Animal studies have been used to investigate the adaptive mechanisms that diseased muscles use in accommodating to exercise training to gain further insight into the fundamental biology of the response.4,49,59

One of the problems in studying the effect of exercise in NMDs is that muscular dystrophies are a heterogeneous group of disorders that have traditionally been classified by clinical phenotype, including mode of inheritance, age of onset, and overall progression of the disease. However, in the last 10 years, an increasing number of defects in specific genes have been identified as the underlying cause of different forms of muscular dystrophy (MD). Most of the genes encode for components of the dystrophin-glycoprotein complex (DGC), an assembly of transmembrane and membrane-associated proteins that form a structural linkage between the F-actin cytoskeleton and the extracellular matrix in muscle. The proteins that comprise the DGC are organized into three subcomponents: the cytoskeletal proteins, the sarcoglycans, and the sarcospan.8,9 Many of the different types of MDs arise from primary mutations in gene encoding components of this complex. Mutations in the dystrophin gene that result in a complete loss of dystrophin, lead to a Duchenne MD (DMD) phenotype. There are at least four sarcoglycan subunits (α, β, γ, and δ) in muscle and mutations that can result in four types of autosomal recessive MD. Alpha laminin-2 (LAMA2) is a basement membrane protein and binds to β-dystroglycan. Mutations in the LAMA2 gene result in the MDC1A type of congenital MD.33,66 It is thought that mutations in components of the DGC complex lead to a loss of sarcolemmal integrity and render muscle fibers more susceptible to exercise-induced damage.

Long before a genetic understanding of the basis of MDs was known, researchers used heredity animal models of MD to examine the effect of exercise on dystrophic muscle. Animal models that have been used in investigations of increased muscle activity include the dystrophic chicken, cardiomyopathic hamster, dy/dy mouse, mdx mouse, and the xmd dog. These and other animal models have been the subject of several recent reviews.1,3,5 Type of inheritance, gene location, affected gene product, and the human correlates are reviewed in Table 1. Species with the same gene pool abnormality often have a different phenotypic expression and even a different gene-chromosome location than humans. The same genetic defect can produce diverse pathologic findings when expressed in different species. Awareness of the gene product function, contractile characteristics, fiber type and pathologic characteristics of each species at various ages are important in evaluating the effect of interventions, since these characteristics are used as criteria when evaluating responses to a given intervention.

The gene location(s) and affected product(s) of the autosomal dominant dystrophic chicken are unknown. White, fast-twitch muscle is the most severely involved. Muscle degeneration does
not become severe until after age 1. The muscles also appear to be myotonic. The dystrophic chicken is now rarely used as an animal model, since there is no known human correlate.

In rodents and in other animals with dystrophy such as the dog, fast-twitch muscles and type 2B fibers are the earliest and most severely affected. However, there is a marked difference between species in pathology, gene location, and gene product. The major organ system involved in the hamster is the heart, while the diaphragm is more severely affected than skeletal muscle in the mdx mouse. The peripheral nerves are also involved in the dy/dy mouse, which is the most severely impaired and has the most rapid disease progression of any of the rodent models of MD, although this may be due in part to the neuropathy. The X-linked recessive mdx mouse lacks dystrophin, similar to young males with DMD. A lack of dystrophin affects the entire DGC. The life span of the mdx mouse is normal and it has minimal clinical muscular weakness. After the initial bout of extensive degeneration at 2 to 4 weeks of age, the muscles almost completely regenerate and exhibit subsequent hypertrophy. However, following this occurrence, the muscles undergo a continuous low level of degeneration and regeneration. Although their functional performance, as determined by contractile studies, progressively declines with age, the changes are relatively mild, even at 2 years of age.

While the skeletal muscle has mild progression, the diaphragm exhibits more severe degeneration and fibrotic infiltration similar to that seen in DMD. The mechanism that causes the mdx mouse diaphragm to have so much evidence of dystrophy while mouse limb muscles do not, has not yet received satisfactory explanation. Gillis proposed that forced lengthening, induced by the elastic recoil of the thorax as the diaphragm contracts during the first half of expiration, induces an eccentric contraction injury. There are likely other mechanisms at play as well. During exercise, the mouse can spare the hindlimb muscles by avoiding activity, yet the diaphragm must continually contract to do the work of breathing. Compared to larger mammals, mice have more muscle power per body weight. During normal activity, mouse limb muscles are not significantly strained. The xmd dog, which also lacks dystrophin, shows overt clinical signs of the dystrophy at 6 to 9 weeks of age. These include weakness, stiff gait, bunny-hopping and increased serum creatine kinase levels. Morphologically, necrosis and regeneration are observed with marked endomysial fibrosis and fiber size variation. The mdx dog has a clinical progression closer to that of DMD than does the mdx mouse. The dog, being a larger mammal like the human, has a relative biomechanical disadvantage compared to the mouse. Thus, for larger mammals with a dystrophin deficient condition, locomotion and other less intense forms of activity may place a great enough burden on skeletal muscle to induce injury and subsequent necrosis.

The autosomal recessive dy/dy mutant mouse (129 ReJ) and the 129B6F1/J hybrid have a deficiency in the laminin alpha 2 chain (merosin) and are considered models for the MDC1A type of congenital MD. There are several other murine models for laminin alpha 2 deficient congenital MD. Skeletal muscle fiber degeneration occurs early and progresses very rapidly in the 129 Re J mutant, and only slightly less so in the hybrid. The life spans vary but are much shorter than normal. Hind-limb paralysis, progressive ataxia and twitching, and scoliosis are apparent as early as 2 weeks of age. There is normal development during the first week postnatal, followed by a severe progression of the disease during the second week of life. During the third week, there is rapid degeneration followed by a relatively stable period between the fourth and eighth weeks of age. Thereafter, there is general fiber atrophy and dedifferentiation of the fiber histochemical profile of the fiber. The phenotype of DMD is more like that of the dy/dy mouse than of the mdx mouse.

The autosomal recessive BIO cardiomyopathic hamster has a mutation in the delta-sarcoglycan gene and is considered a model for one type of autosomal recessive limb-girdle MD. The life span of the cardiomyopathic hamster is about 12 months and it has no obvious locomotor physical disability at the time of death from cardiomyopathy. In the early phase (1 month) and mid-phase (4 to 6 months), the fundamental pathologic events are repeated cycles of segmental necrosis of groups of fibers, followed by vigorous regeneration.

Many of the exercise experiments on animal models of MD were performed before there was an understanding of the underlying genetic defects. These experiments were typically conducted to simulate exercise training or to study contraction-induced injury. The objective of the exercise training studies was primarily to compare the adaptations of normal and dystrophic muscle to exercise. The studies of contraction-induced injury utilized vigorous short-term exercise testing or simulated exercise to determine whether dystrophin-deficient muscles were more susceptible to injury than normal muscles.

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**TABLE 1** Animal models used in exercise investigations

<table>
<thead>
<tr>
<th>Inheritance</th>
<th>Human Gene Location</th>
<th>Affected Gene Product</th>
<th>Human Correlate</th>
</tr>
</thead>
<tbody>
<tr>
<td>mdx mouse and xmd dog</td>
<td>XR Xp21.2</td>
<td>Dystrophin &amp; associated dicycoproteins</td>
<td>DMD/BMD</td>
</tr>
<tr>
<td>dy/dy mouse</td>
<td>AR 6q2</td>
<td>Laminin-N (merosin)</td>
<td>Congenital muscular dystrophy</td>
</tr>
<tr>
<td>Hamster</td>
<td>AR 5q33-q34</td>
<td>Delta sarcoglycan</td>
<td>SCARMD-LGD</td>
</tr>
<tr>
<td>Chicken</td>
<td>AD Unknown</td>
<td>Unknown</td>
<td>None</td>
</tr>
</tbody>
</table>

AD = autosomal dominant; AR = autosomal recessive; DMD/BMD = Duchenne and Becker muscular dystrophy; LGD = limbagride dystrophy; SCARMD = Severe childhood autosomal recessive muscular dystrophy; XR = X-linked recessive.
EXERCISE TRAINING: WHAT DOES EXERCISE DO TO DISEASED MUSCLE?

Regardless of differences in methodology, the objective of most of the following investigations was to evaluate the effect of exercise training on functional performance, muscle contractile characteristics, and muscle pathology. Animal models included the dystrophic chicken, cardiomyopathic hamster, dy/dy mouse, and mdx mouse. With the exception of only one study, exercise training consisted of high-repetitive, aerobic type activity (e.g., swimming, treadmill running, and voluntary-wheel running). Daily exercise intensity ranged from submaximal exercise to maximal exhaustive exercise. The exercise protocols ranged from 1 week to several months. There was also marked variability in the age of the animals at the initiation of the studies and, hence, variability in the degree of muscle degeneration and regeneration at baseline. In most investigations, the number of animals was adequate, and nonexercised dystrophic animals, normal animals, and exercised normal animals served as control subjects.

**Dystrophic Chickens**

In the investigations using dystrophic chickens, rotating cage exercise or righting practice were reported to improve functional ability, but did not retard the muscle atrophy.3,44,60

**Dystrophic Hamster**

There have been three swimming studies, one weight-lifting exercise study, and three treadmill studies of the cardiomyopathic hamster. Homburger and colleagues reported that swimming to exhaustion for 8 days accelerated cardiac and skeletal necrosis,40 and colleagues examined the effect of swimming with tail weights for 30 to 60 minutes per day for 8 weeks on the histopathology of the heart.39 Greater calcium necrosis was found in the heart of the exercised hamsters than in the heart of the nonexercised control subjects. Sembrowich and colleagues examined the effect of 18 weeks of vigorous treadmill exercise.63 The results indicated a beneficial contractile response in the heart, while there was no difference in the skeletal muscle weight or severity of skeletal muscle necrosis after exercise.

In young developing hamsters, vigorous treadmill running for 2 hours per day for 1 month had no effect; while running for 4 hours per day for 1 month resulted in significant increases in muscle tension and less muscle necrosis in both fast and slow-twitch muscles. There was an increase in the oxidative capacity of the skeletal muscles, with hypertrophy of type 1 fibers, an increase in the percentage of type 1 fibers in slow-twitch muscles, and an increase in the number and area of type 1 fibers of the plantaris muscles.28

In the only animal investigation using resistive exercise training, Howells and Goldspink subjected hamsters at 9 weeks to a progressive weight lifting program for 5 weeks.41,42,43 Nonexercised hamsters had decreased fiber size and area, while the exercised hamsters had an increase in fiber size and area, and an increase in succinic dehydrogenase activity in fast and slow twitch muscles. No 21-week-old hamsters exhibited these changes, but 45-week-old hamsters exhibited a decrease in fiber size, fiber area, and succinic dehydrogenase activity.

After 4 weeks of vigorous treadmill running, the cardiomyopathic hamsters failed to increase their myoglobin concentration in the same manner as normal hamsters.7 Tate and colleagues found that one bout of swimming to exhaustion had no effect on cardiac or skeletal muscle, calcium uptake, or adenosine triphosphatase adenine triphosphatase Pase activity.67

**Laminin-deficient dy/dy Mouse**

There have been three swimming, one voluntary-wheel running, and two treadmill exercise investigations in the dy/dy mouse. Ages at the start of the exercise programs ranged from 3 to 14 weeks, and the exercise programs lasted from 6 days to 5 weeks.

In functional performance studies, dy/dy mice produced less work and power and had lower levels of fatigue resistance than normal mice.34 The dy/dy mice also swam or ran more slowly and developed a higher percentage of muscle fibers with large diameter.35,64

In a voluntary wheel running study, Hayes and colleagues compared 4-week-old exercised dy/dy, mdx, and C57 mice with their sedentary control subjects.35 The mdx and C57 mice ran for 16 weeks, while the dy/dy mice ran for 5 weeks. The difference in performance between species was marked. The C57 mice ran 6.5 km/day, mdx mice ran 1.6 km/day, and dy/dy mice ran only 0.5 km/day. The exercised mdx and dy/dy mice produced increased tension and exhibited less fatigue resistance in fast-twitch muscle as compared to their sedentary controls. There were no significant changes in slow-twitch muscle. Several dy/dy mice with extremely reduced hind limb function died before the end of the experiment. The results from these animals were not included in the study.

In a study by Taylor and colleagues, 2 weeks of maximal treadmill running resulted in a marked decrease in slow-twitch muscle tension as compared to sedentary controls.58 There was high mortality in the more severely involved mice. In a related study Fowler and colleagues reported that 3 weeks of submaximal treadmill running resulted in increased slow muscle fiber twitch tension, increased rate of twitch tension development, and increased rate of twitch tension relaxation.30 There was no change in the contractile properties of the fast-twitch muscle. However, exercise significantly retarded the histopathologic progression of the disease in both fast-twitch and slow-twitch muscles. There was a reduction in the variability of the fiber sizes in the type 1 fibers of the slow-twitch soleus muscle and the type 2B fibers of the fast-twitch extensor digitorum longus (EDL) muscle.

In a simulated exercise study, Luthert and colleagues subjected dy/dy mice to low frequency (10 hz) electrical stimulation for 1 week.52 This stimulation resulted in increased tensions of slow and fast-twitch muscle when compared to the control contralateral muscles. The succinic dehydrogenase activity of the stimulated
muscles also was increased. A similar electrical stimulation study by Dangain and Vrbova resulted in a speeding of the time course of the muscle contraction and an increase in the fatigue resistance of skeletal muscles. There was an increase in the force output of weak dystrophic muscles with smaller fibers, but a slight decrease in force output of the relatively strong dystrophic muscles. It was suggested that stimulation promotes growth and development of small regenerating fibers and induces an increase in the mitochondrial content of the muscle fibers.

**Dystrophin-deficient mdx Mice**

There have been four voluntary wheel-running studies and three swimming investigations in the mdx mouse. Ages at the start of the exercise program ranged from 3 weeks to 2 years, and the exercise periods lasted from 4 to 52 weeks. Several drug-exercise studies were also performed in this study.5,26,37,45,76

Hayes and colleagues in a 15 week endurance swimming program that started with the mice at 5 weeks of age, observed increased tension, increased fatigue resistance, and a greater percent of type 1 fibers in the soleus of the exercised mdx mice. The EDL muscles exhibited a longer half-relaxation time and an increase in the number of type 2A fibers. Lynch, using the same swimming exercise protocol, measured the contractile properties of skinned fibers. Type 2B fibers from the EDL and type 2A fibers from the soleus of exercised animals were found to be less sensitive to Ca++ and Sr++ when compared to sedentary mice. In a 1998 study, Hayes and colleagues examined the effects of a 10 week, once a day endurance swimming protocol using adult (8 to 10 months) and older (24 months) mdx and C57 mice. The exercised mice had increased tension per cross sectional area in both the soleus and the EDL, but there was no effect on body mass, fatigue properties, muscle mass, or fiber type profiles in either muscle.

Ten to 12 months of voluntary wheel running increased the maximal tetanic tension and the contraction time of the mdx diaphragm, but had no effect on the slow twitch soleus muscle. Carter and colleagues examined the effect of 4 weeks of voluntary wheel running in mdx and C57 mice using two different age groups, young (4 weeks of age) and adult (6 months of age). The young mdx mice ran 78% of the distance run by the C57 mice, while the adult mdx mice ran only 31% of the distance run by the C57 mice. After exercise, the slow-twitch soleus muscle of both the young and the old mdx mice exhibited hypertrophy with no change in tension per cross sectional area and no change in fatigue resistance. The mdx EDL exhibited slight hypertrophy and loss of tension in the adult, while the young exhibited no changes. There was a significant increase in serum levels of creatine kinase in the adult exercised mdx mice when compared to their sedentary controls. Hayes and Williams reported that 16 weeks of voluntary wheel running beginning at 4 weeks of age resulted in hypertrophy of the soleus and an increase in soleus tension, fatigue resistance, and proportion of type 1 fibers. In the EDL, there was no effect on tension but there was an increase in fatigue resistance and a conversion to oxidative fiber types. Wineinger reported that 12 months of voluntary wheel running slightly increased the fatigue resistance of fast-twitch EDL muscles, but had no effect on their tension development.74

Biondi and colleagues recently showed a slower rate of disease progression and postnatal motor unit (MU) death in a type 2 spinal muscular atrophy-like mice. Physical exercise (running) delayed motor neuron (MN) death and lead to an increase in the postnatal maturation rate of the MUs. Exercise training also enhanced the expression of the gene encoding the major activating subunit of the NMDA receptor in MNs, namely the NR2A subunit (which is dramatically down-regulated in the spinal cord of type 2 SMA-like mice).

A recent study showed that exercise improves graft success and hybrid fiber distribution within mdx muscle. Muscle precursor cells were transplanted into tibialis anterior (TA) muscles of mdx mice using a single injection trajectory. During the follow-up weeks, muscle fiber breaks were induced by making mdx mice swim. Twenty minutes of swimming was used to induce damage in about 30% of TA muscle fibers. Graft success, evaluated as the percentage of hybrid fibers which are eGFP(+), was improved by 1.9-fold after swimming 3 times per week during 4 weeks and by 1.8-fold after daily swimming. Hybrid muscle fiber transversal and longitudinal distribution were also increased after repeated physical efforts. Exercise-induced fiber breaks, which improved muscle precursor cells recruitment and fusion, and increased long-term graft success as well as transverse and longitudinal distribution of hybrid fibers.

Dystrophin, which is absent in muscles of the mdx mouse, is thought to stabilize the sarcolemma during contractions of normal muscle. This is supported by studies which have shown transient localized plasma membrane instability in dystrophin-deficient fibers. Carter and colleagues investigated the use of intravenously injected fluorescent dextran molecules (FDx) as a histological marker of sarcolemmal injury in dystrophin-deficient mdx and control mice. Using fluorescent microscopy, uptake of FDx was assessed in sections of quadriceps muscles from three models: non-exercised normal mice, normal mice run downhill (0, 3, and 7 days post exercise), and non-exercised mdx mice. In non-exercised normal muscles, strong intercellular fluorescence was seen between fibers. In normal mice run downhill, only small amounts of intracellular FDx were observed within cells of the quadriceps from day 0 and 3 post exercise, but not at day 7. With hematoxylin and eosin (H&E) staining, no muscle pathology was observed at day 0, slight pathology was observed at day 3, and regeneration was observed at day 7. In contrast, extensive intracellular FDx was observed within the muscles of the mdx mice, particularly in fibers that appeared pre-necrotic on H&E stained sections. In studies using exhaustive exercise and electromyography (EMG), significant evidence of sarcolemmal damage and instability in both mdx and myotonic (mto) mice was shown. In the mto mice, membrane instability was not helped by blocking the fast sodium channels with amitriptyline, procainamide, and phenytoin, indicating that the leaks may not be coming through a known or existing membrane ion channel and could be novel, exercise-induced damage. Newer agents like mexilitine have not been tried.
in this model however. A similar phenomenon is particularly evident in mdx diaphragm.\(^{12}\) Interestingly, some of this phenomenon is also seen in neuropathic mice.\(^{55}\)

Several investigators have examined the effect of different types of running exercise on the susceptibility to injury on various animal models of MD. In the canine model (CXMD), Valentine and colleagues showed that even mild exercise can cause significant elevation of serum creatine kinase that reached a peak at 4 hours post exercise and returned to baseline values at 24 hours post exercise.\(^{69}\) Sandri and coworkers demonstrated that the apoptotic index in mdx mice dramatically increased after short-term wheel running, whereas in the skeletal muscle of control mice only a minor increase in apoptotic cells was detectable.\(^{62}\) This was the first evidence that exercise may trigger the apoptosis in dystrophin deficient mice. Using fluorescent dye, Clarke and colleagues examined triceps muscles of mdx mice after a single bout of downhill running.\(^{20}\) Seventy-five percent of the fibers of the mdx triceps exhibited transient membrane disruptions which was 7-fold greater than control mice. Furthermore, no difference was observed between muscles of control mice following running and those of non-exercised control mice. Brusee examined the effect of downhill running for 3 days on the histology of mdx mice.\(^{61}\) A 31% increase in positive staining for Evans blue muscle in young mdx mice was reported while there was only up to a 3% increase in staining in normal muscle. Stained fibers were also present in 2% to 15% of non-exercised mdx mice. Further evidence of injury and repair was shown by Vilquin, who investigated skeletal muscle fibers in transgenic dystrophinless mice expressing beta galactosidase.\(^{73}\) Adult mdx/beta galactosidase (dystrophin negative) and normal/beta galactosidase (dystrophin positive) mice were submitted to one short session of eccentric, downhill running exercise. The leakage of creatine kinase and beta galactosidase was investigated prior to, 1 hour after, and 3 days after the running session. A significant and transient rise in the level of these enzymes was noted in the serum of mdx mice following the exercise session. The peak leakage was transient, suggesting that muscle fiber lesions were rapidly repaired following this short, noninvasive eccentric running session. All of these running experiments revealed increased susceptibility to injury in dystrophic animals as compared to control subjects. It is important to note that transient damage is the stimulus for adaptation. Many acute exercise induced damaged studies have been erroneously misinterpreted as suggesting that exercise training is not good for dystrophic muscles, as the exercise does lead to evidence of muscle damage. This same philosophy has led some investigators to suggest that the acute increase in oxidative stress seen after a single bout of exercise may be deleterious. Yet it would appear that exercise training actually lowers oxidative stress in mdx mice.\(^{2,11,46}\)

All of the investigations used repetitive exercise training protocols, usually submaximal wheel running or swimming, with the exception of one investigation, which used a resistive strengthening training protocol. Regardless of species and differences in methodology, all of these investigations reported a relatively normal and beneficial adaptation to aerobic exercise. The benefits of the high-repetitive, low-impact training, whether by running, swimming, or electrical stimulation, typically has a greater effect on the more oxidative fibers and may reduce the risk for further mechanical damage to these fibers. However, this type of training had little impact on fast-twitch fibers. The major factors determining the beneficial or deleterious effect of exercise training in animals with MD include: (1) the age of the animal at the start of the study, (2) the severity of the dystrophy at the start of the study, (3) the intensity of the training (sub-maximal or maximal), (4) the length of the training, and (5) the type of training (repetitive aerobic or resistive strength). These factors are similar to those reported in humans with dystrophy.

Studies have demonstrated that mechanical weakness and contraction-induced muscle injury are not always required for muscle degeneration and the dystrophic process. Evans blue dye, which does not cross into skeletal muscle fibers in normal mice, shows marked accumulation in the muscles of mdx mice and in muscles of transgenic mice bearing different dystrophin mutations. However, the muscles of the dy/dy mouse, which have defects in the laminin alpha 2-chain, an extracellular ligand of DGC, showed little dye accumulation.\(^{66}\) There was no evidence for contraction-induced injury in mice lacking γ-sarcoglycan that were subjected to an extended, rigorous exercise regimen.\(^{33}\) Isolated muscles lacking γ-sarcoglycan have shown normal resistance to mechanical strain induced by eccentric muscle contraction with normal peak isometric force generation.

Regardless of species and differences in methodology, the majority of these investigations reported that dystrophic animals had a normal and beneficial adaptation to mild, submaximal aerobic exercise, while maximal exhaustive exercise had a deleterious effect, especially to fast-twitch muscle. The beneficial adaptations to mild aerobic exercise training included an increase in muscle strength and a reduction in muscle degeneration. There was a hypertrophic response in the muscles that were not severely affected by the dystrophy. High repetitive, low impact exercise increased the oxidative capacity and the proportion of oxidative fibers, especially in slow-twitch muscles. Younger animals tend to benefit more from exercise studies than older animals. However, high-repetitive exercise typically had no effect or a deleterious effect in fast-twitch muscles that were more severely affected by the disease and are more likely to incur damage by eccentric exercise. There are not enough reports examining the effect of high-resistive strength training exercises in dystrophic animals to allow any conclusions to be drawn.\(^{11}\)

It is now well accepted that dystrophinopathies confer increased susceptibility to oxidative stress, both in human and animal models. Tarnopolsky’s group recently examined the effect of low intensity exercise training (LIT) on markers of oxidative stress in skeletal muscle of mdx and wild-type mice.\(^{46}\) LIT was associated with lower levels of malondialdehyde and protein carbonyls in white muscle of mdx mice (decreased 38% and 44%, p<0.001 and p<0.01, respectively). Antioxidant and mitochondrial enzyme activities were higher in white muscle of mdx than in wild type mice (p<0.05). LIT in mdx mice induced physiological adaptation, resulting in lower levels of markers of oxidative stress to levels that did not differ from those of wild type mice.
Most of the exercise studies using animal models of MD were performed with the assumption that they were models of DMD. However, it is known that some of these animal models were more similar to other MDs. The dy/dy mouse is a model of one of the congenital MDs, the BIO hamster is a model of one of the limb-girdle MDs, while the mdx mouse and xmd dog are models of DMD. With the advent of genetic techniques, models that have the same genetic defect as their human counterpart can now be studied. Identification of the defect and understanding the role of the gene product will help us elucidate the role of exercise in NMD. In the future, current knowledge of the response of diseased muscle to exercise will provide a benchmark to compare the possible benefits of corrective gene therapy.

HUMAN STUDIES

Human studies examining the effects of exercise in subjects with NMD are difficult at best for many reasons. One of the problems in studying the effect of exercise in NMDs is that MDs are a heterogeneous group of disorders that have traditionally been classified by clinical phenotype, including mode of inheritance, age of onset, and overall progression of the disease. These are also relatively uncommon, if not rare, disorders. Thus, unfortunately, much of the existing literature mixes myopathic and neuropathic subjects together, likely to simply increase sample sizes. In slowly progressive NMDs a 12-week, moderate-resistance (30% of maximum isometric force) exercise program resulted in strength gains ranging from 4% to 20% without any notable deleterious effects.

In a mixed population of subjects with myopathies and neuropathies, a 12 week home aerobic program also improved endurance. However, in the same population, a 12-week, high-resistance exercise program (training at the maximum weight a subject could lift 12 times) showed no further added beneficial effect compared to the moderate resistance program and there was evidence of overwork weakness in some of the subjects. In a comparative study, patients having Charcot-Marie-Tooth (CMT) disease appeared to benefit significantly from a strengthening program; whereas myotonic MD (MMD) (DM1) patients showed neither beneficial or detrimental effects. Tarnopolsky’s group also duplicated some of Kilmer’s earlier findings on resistance training, although in this study, they isolated the study group from patients with CMT only, as opposed to mixing all diagnoses. It is clear that there are differences between myopathic and neuropathic subjects, as was demonstrated nicely by Lindeman and coworkers. The myotonic group (DM1) group showed neither positive nor negative effects of the moderate resistance training protocol, whereas in the CMT groups, the training produced a moderate increase in strength and leg-related functional performance.

Due to the active muscle degeneration in the rapidly progressive NMDs like DMD or amyotrophic lateral sclerosis (ALS), the risk for overwork weakness is great and exercise should be prescribed cautiously using a common sense approach. All patients with NMD should be advised not to exercise to exhaustion due to the risk of muscle damage and dysfunction. Patients participating in an exercise program should be cautioned of the warning signs of overwork weakness, which include feeling weaker rather than stronger within 30 minutes post exercise, or excessive muscle soreness 24 to 48 hours following exercise. Other warning signs include severe muscle cramping, heaviness in the extremities, and prolonged shortness of breath.

Early intervention with gentle, low-impact aerobic exercise such as walking, swimming, and stationary bicycling improves cardiovascular performance, increases muscle efficiency, and lessens fatigue. Based on the available investigations, there is adequate evidence to generally advocate a submaximal strengthening program for persons with slowly progressive NMDs. There seems to be no additional benefit to high-resistance, low-repetition training sets, and the risk of actually increasing weakness becomes greater. Improvement in strength hopefully translates to more functional issues such as improved endurance and mobility.

Tarnopolsky’s group has shown this type of effect in healthy young men recovering from exercise-induced muscle damage. Subjects (n = 4) performed 300 maximal eccentric contractions, and skeletal muscle biopsy samples were analyzed at 3 hours and 48 hours after exercise. Changes in gene expression were studied 3 hours and 48 hours post exercise. By 48 hours post exercise, 59 genes had increased activity while 29 had decreased. Based on that initial data, 19 gene changes were selected and a subsequent analyses was conducted using real-time polymerase chain reaction on muscle biopsy samples taken from a larger number of subjects (n = 11) who performed an identical bout of exercise to induce muscle damage. This led to a rapid (3 hour) increase in sterol response element binding protein 2 (SREBP-2), followed by a delayed (48 hour) increase in the SREBP-2 gene targets Acyl CoA:cholesterol acyltransferase (ACAT)-2 and insulin induced gene 1 (insig-1). The expression of the IL-1 receptor, a known regulator of SREBP-2, was also elevated after exercise. This data clearly shows that human skeletal muscle growth and remodeling due to severe exercise is under direct regulatory control and that exercise does induce significant alterations in steady state mRNA content gene. The novel genes identified here are likely involved the ones in recovery from exercise—induced damage. This lends credence to the concept that even a single bout of exercise can lead to profound cellular adaptations, even at the gene expression level. Ultimately these rapid adaptations may help the muscle become increasingly resistant to future damage from future bouts of exercise. How this would play out in diseased muscle is still unclear and more rigorous studies in larger groups of subjects are needed before conclusions can be drawn with any degree of confidence.

Krivickas’s group recently conducted a Cochrane review of exercise in randomized or quasi-randomized controlled trials of people with a diagnosis of definite, probable, probable with laboratory support, or possible ALS, as defined by the El Escorial criteria. This included progressive resistance or strengthening exercise and endurance or aerobic exercise. The control condition was no exercise or standard rehabilitation management, and the primary outcome measure was improvement in functional ability, decrease in disability or reduction in rate of decline, as measured by a validated
outcome tool at 3 months. Secondary outcome measures included the improvement in psychological status or quality of life, decrease in fatigue, increase in, or reduction in rate of decline of muscle strength (strengthening or resistance studies), increase in, or reduction in rate of decline of aerobic endurance (aerobic or endurance studies) at 3 months and frequency of adverse effects. They identified two randomized controlled trials that met inclusion criteria. The first examined the effects of a twice-daily exercise program of moderate load, endurance exercise versus "usual activities" in 25 people with ALS. The second examined the effects of thrice weekly moderate load and moderate intensity resistance exercises compared to usual care (stretching exercises) in 27 people with ALS. After 3 months, when the results of the two trials were combined, there was a significant weighted mean improvement in the Amyotrophic Lateral Sclerosis Functional Rating Scale measure of function in the exercise compared with the control groups (3.21, 95% confidence interval 0.46 to 5.96) in favor of the exercise group. No statistically significant differences in quality of life, fatigue, or muscle strength were found.

A similar Cochrane review was done for strength training or aerobic exercise programs in patients with muscle disease. The goal was to examine the efficacy and safety of strength training and aerobic exercise training in patients with muscle diseases. To be included in the review, the studies had to be randomized or quasi-randomized controlled trials comparing strength training and/or aerobic exercise programs, lasting at least 10 weeks. They only identified two randomized trials fulfilling all inclusion criteria. The first trial compared the effect of strength training versus no training in 36 patients with myotonic dystrophy. The other trial compared strength training versus no training combined with albuterol or placebo in 65 patients with facioscapulohumeral MD (FSHD). The authors concluded that in myotonic dystrophy and FSHD moderate-intensity strength training does not appear to do harm but there is insufficient evidence to establish that it offers benefit. Limitations in the design of studies in other muscle diseases prevent general conclusions in these disorders.

Another recent study which noted that pain and fatigue are important features in FSHD, tried to assess strength training and albuterol in this disease, but ultimately concluded that these modalities do not have a positive or negative effect on pain, the extent of fatigue experienced, functional status, and/or psychological distress.

CONCLUSION

One may conclude from strengthening studies in these diverse populations of neuromuscular patients that with moderate resistance training, overuse weakness and muscle damage likely does not occur in muscles with ≥ 3/5 strength (Medical Research Council scale). Thus, strength gains may be achieved, although they are not as great as they would be in subjects without a NMD. Strength gain would appear to be roughly proportional to the initial muscle strength, suggesting that a strengthening program should be initiated as early as possible in the course of the disease. High-resistance eccentric exercise should be avoided as it may produce muscle damage. However, it should be noted that no studies of strength training in neuromuscular patients have demonstrated translation of the modest strength gains achieved into improved function in activities of daily living or the overall course of the disease. Nonetheless, it would be prudent to recommend beginning a strengthening program as soon as possible after an NMD diagnosis. The objective of such a program is to maximize the strength of unaffected or mildly affected muscles in an attempt to delay the time at which function becomes impaired. Weight training or strengthening exercise should be performed with a weight that the individual can lift 20 times; this is a simple way for the patient to select a weight that is in the 20% to 40% of maximum voluntary contraction range (alternatively selecting a weight the NMD patient can lift 20 times and then do sets of 10 repetitions. This assures that one remains within this range). The patient should then perform 2 or 3 sets of 10 repetitions. This guideline will prevent overworking the muscles with excessively heavy weights. Another general guideline is that if an exercise regimen consistently produces muscle soreness or fatigue lasting longer than one half hour after exercise, it is too strenuous.

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Measuring and Promoting Physical Activity in a Free-living Environment in Persons With Neuromuscular Diseases

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INTRODUCTION

Most clinicians treating ambulatory patients with diseases affecting the peripheral nervous system support the promotion of physical activity in order to maintain and hopefully increase energy expenditure as well as retard the effects of a sedentary lifestyle and deconditioning. With increases in lifespan, secondary conditions such as diabetes mellitus and cardiovascular disease are of greater relevance. Unfortunately, there is a paucity of literature that explores methods of appropriately recommending and monitoring physical activity in patients with mobility limitations.

The differences between physical activity and energy expenditure must be fully understood. One parameter cannot be directly inferred from the other. Physical activity represents muscular movement, while the energy expenditure that is associated with the movement may be a reflection of age, gender, body mass, and movement efficiency. In physical disabilities, this last factor may be the greatest cause of discrepancies from those who are able-bodied, as well as provide an opportunity for intervention. For example, energy expenditure will be increased in a patient with bilateral ankle dorsiflexor weakness from peripheral neuropathy during gait, but may be markedly reduced with the use of ankle-foot orthoses.

Traditionally, investigators devised exercise intervention studies involving persons with neuromuscular diseases (NMDs) to demonstrate improvement in strength and/or endurance. Gains in these areas could be extrapolated to presumed benefits in mobility, energy expenditure, functional activities, and quality of life in the home and community. There is minimal experimental evidence to support these assumptions. Motivating sedentary able-bodied adults to become more active is challenging. Therefore, with additional issues relating to muscular weakness, fatigue, and possible cardiopulmonary disease involvement, persons with NMD have major additional hurdles to overcome.

Ideally, clinicians and researchers are interested in daily activities in the patient’s own home “free-living” environment. The gold standard for measurement of free-living total energy expenditure associated with physical activity is the doubly labeled water technique. The technique, however, is cumbersome, expensive, and provides no information about patterns of physical activity. Other investigators have used laboratory measures such as timed up-and-go or 6-minute walk tests. The difficulty with extrapolation in regards to a person’s home and community still exists with these measures, since they are performed in an artificial environment and deal with potential, rather than actual activity.

Self-reported physical activity diaries have shown poor correlation with objective measures of activity. A few studies have utilized indirect markers, such as the SF-36, a life satisfaction survey. Although this provides useful information of a person’s perceived health status, it too, is of poor correlation with day-to-day physical activities. Newer quantitative methods to measure physical activity in a free-living, community and home environment will be addressed. These tools can potentially be used to measure the practical effects of a rehabilitation intervention, or be used as a method to stimulate physical activity while providing feedback to both the patient with NMD as well as the clinician. The selection of a measurement device is dependent on what information a clinician is attempting to collect. Some devices simply count steps, measure the intensity of activity, or estimate total daily energy expenditure. The latter is typically favored in a research setting.

Pedometry

Pedometers are typically worn on the waist and measure the number of steps taken over a given time period, typically a day. Three consecutive days of data are generally sufficient to reflect the typical daily variation in ambulation. The devices are inexpensive ($10-$50), easy to use, and well suited for larger population studies. Accuracy and reliability have been demonstrated in able-
bodied populations; however, concerns exist about their reliability in the presence of abnormal gait and very slow gait speeds.\(^9,10\)

In nondisabled populations, investigators have shown inverse correlation between steps/day and body-mass index (BMI) measurement, as well as components of the metabolic syndrome.\(^6\) Typically, these populations average around 7000 steps/day (with a large standard deviation), while those with chronic diseases average less than 5500 steps/day.\(^26\) Although a goal of 10,000 steps/day has been proposed as a method to decrease obesity and diabetic/cardiovascular risk factors in the general population, there is no strong research support for this claim. For research purposes in disabled populations, the greatest limitations for pedometry involve accuracy issues, an inability to measure the intensity of ambulatory activity, and the resultant inability to accurately measure free-living energy expenditure.

### Heartrate Monitoring

One experimental method used to indirectly measure energy expenditure is continuous heartrate (HR) monitoring, particularly when coupled with calibration to VO\(_2\) at a given HR in the laboratory. The obvious limitation is a lack of tight correlation of HR to physical activity in community settings, which is dependent on the catecholamine state of the subject. Typically, HR monitoring underestimates energy expenditure as compared to other methods. Although cumbersome, combining HR monitoring with a motion sensor may yield a strong relationship to free-living energy expenditure.\(^23\)

### Accelerometry and Energy Expenditure

In order to measure different types of physical activity that are not limited to ambulation, accelerometers attached to the beltline or waistline may be used to measure motion in three planes. Physical activity is measured in terms of “activity counts” which can be stratified by intensity (e.g., activity count/specific time interval). Accelerometers are more costly ($75-$800) than pedometers, but are believed to provide a better estimation of energy expenditure with continuous 7 day measurement. Limitations include the inability to exclude passive movement counts due to activities such as riding in an automobile or on a bicycle, and the inability to define the specific activity that is associated with the count. Accelerometry has been used in numerous studies to estimate energy expenditure associated with physical activity. Unfortunately, most investigations have not shown agreement with the criterion standard doubly labeled water method, emphasizing the difficulty in converting body movement to energy expenditure on an individual basis.\(^15\) There have been no studies to date that use beltline or waistline accelerometry to measure patterns of activity in persons with NMD, and it is unknown how abnormal gait impacts activity counts.

### Step Activity Monitoring

Step activity monitoring devices represent a type of accelerometry that is specifically designed for ambulation. This method of mobility assessment overcomes many limitations of the waist attached pedometers. The most frequently used device in the literature is the StepWatch\textsuperscript{TM} step activity monitor (SAM).\(^7\) It can be calibrated according to height, cadence, and walking style of the individual. In addition to total number of steps, the intensity of activity can be measured by recording the number of steps in a predetermined time interval as low as 6 seconds (Table 1). The measure of reliability and validity as compared to HR monitoring has been demonstrated in able-bodied adults as well as in children and adolescents.\(^17,20\)

<table>
<thead>
<tr>
<th>Activity Level</th>
<th>Steps/Minute</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactive</td>
<td>0</td>
<td>Watching television, playing computer games</td>
</tr>
<tr>
<td>Low</td>
<td>1-15</td>
<td>Intermittent steps taken during activities of daily living such as moving about the house</td>
</tr>
<tr>
<td>Medium</td>
<td>16-30</td>
<td>Slow walking or moderate activity</td>
</tr>
<tr>
<td>High</td>
<td>&gt;30</td>
<td>Continuous walking or running for part of the time interval</td>
</tr>
</tbody>
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The device appears to provide accuracy in the presence of an abnormal gait. The SAM has an electronic filter to reject extraneous signals, adjust parameters of threshold, cadence, and motion to enhance sensitivity in a wide variety of gait styles. Several studies have examined the accuracy of the device in hemiparetic gait. The SAM was highly accurate for quantifying ambulatory activity in stroke patients as compared to the pedometer\(^16\) and conventional accelerometer.\(^11\) However, there may be some error when the device is attached to the paretic limb while walking over a variety of outdoor terrains.\(^19\) An overall accuracy of 97% to 99% was shown when the SAM was used in persons with lower-limb amputation\(^7\) and incomplete spinal cord injury.\(^2\) In a study of 10 adult subjects with a variety of NMD, the step activity monitor demonstrated good reliability.\(^4\) Neurologic patients had reduced daily step counts, with moderate correlation between gait speed and 7 day mean step counts. A larger follow-up study (n=74), with neurologic patients grouped by type of neuromuscular (NM) pathology, also revealed that decreased step counts and self-selected gait speeds were significant predictors of daily mean step count.\(^5\) All subjects had significantly weaker knee extensors and/or flexors than control subjects.

McDonald and colleagues demonstrated that boys with Duchenne muscular dystrophy (DMD) walked fewer steps/day and spent fewer minutes/day at moderate and high step rates than age-matched controls (Figure 1).\(^18\) In the DMD group, the number of steps correlated with knee extensor strength normalized for body mass. The DMD group also had a significantly higher baseline HR, and showed less increase in HR with increased step rate. Similar findings of a decreased number of steps and less time spent at higher step rates were found in adults with various types of slowly progressive NMD as compared to control subjects (unpublished data) (Figure 2).
Klein and colleagues examined SAM-determined and perceived activity levels in polio survivors in a post-polio (PPS) group and nonPPS group as compared to controls. Subjects in the PPS group averaged the fewest number of steps/day, followed by nonPPS subjects and the control groups. Although perceived activity of the PPS group decreased over the 3 year study period, there was no change in average daily walking activity. Preferred walking speed in this group was close to maximal speed. Thus, the polio survivors ambulate with minimal physiologic functional reserve.

Step Measurement as a Method to Increase Physical Activity

Diet and moderate exercise in the form of walking 30 minutes/day, most days of the week has been linked to healthful outcomes (reduction in BMI, blood pressure [BP], total cholesterol) in able-bodied overweight populations. A recent review of studies using pedometry as a motivational tool to increase physical activity found that pedometer use is associated with significant increases in physical activity of about 2000 steps/day. Individuals found benefit in setting a personal step goal and using a step diary to record progress. After pooling the studies, pedometer users significantly decreased BMI and systolic BP. Therefore, increased physical activity appears to directly translate into beneficial health outcomes.

Pedometry was used as a community-based intervention to increase physical activity in ambulatory adults with slowly progressive hereditary NMD. After baseline measurements were recorded, subjects were instructed to increase physical activity (via daily step counts) by 25%. The use of quantitative feedback appeared to be effective, as a significant increase in daily step activity was noted (Figure 3). Six months following the protocol, the number of steps/day was still increased from the baseline count, but no longer reached statistical significance. In overweight/obese subjects with Type II diabetes mellitus, provision of a pedometer with step goals resulted in an average increase of 3000 steps/day. Thus, it appears that an activity prescription using a pedometer may help to provide a clear goal and effective feedback in the ambulatory disabled.
Unresolved issues in the consideration of pedometry for the disabled include the impact of gait inefficiencies and mobility limitation on creating a realistic recommendation for a specific patient. For example, a patient with myopathy in which even household ambulation severely taxes the muscular and cardiovascular systems is not going to be able to meaningfully achieve significant increases in physical activity with activity prescription. Additionally, it may be assumed that increased physical activity improves glycemic control and reduces cardiovascular risk factors in patients with NMD. However, the increased number or percentage of steps/day required to impact risk factors is unknown. The aforementioned study in which subjects with NMD increased steps by 24% did not result in significant reduction of metabolic syndrome risk factors. Finally, the relationship between self-selected gait speed and community walking activity in persons with NMD requires further investigation.5

CONCLUSION

In summary, quantitative activity devices are a useful real-world tool in determining the extent of sedentary versus active behaviors of patients in their homes and communities. Simple pedometry may be highly effective as a motivational tool. As a research tool for clinical intervention studies, investigators should consider utilizing a device that is more accurate and sensitive to change by stratifying physical activity by intensity. For this indication, step activity monitoring appears to provide a clinically meaningful outcome measure in testing the effectiveness of therapeutic interventions in persons with NMDs.

REFERENCES