Opening the Black Box: The Mysteries of Therapeutic Exercise Unlocked...

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OBJECTIVES  After attending this session participants will (1) know the different forms of therapeutic exercise, (2) know the difference between therapeutic exercise versus lay perceptions of exercise, (3) understand how proper performance of exercise influences exercise efficacy, (4) understand how diagnosis-specific exercise influences exercise efficacy for musculoskeletal conditions, (5) understand how exercise influences nerve and muscle function at a metabolic level in health and disease, (6) be able to choose when exercise is appropriate for their patients with neuromuscular disease, and (7) understand the role of exercise in optimizing physical performance in sports.

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

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What is the Role of Exercise in Low Back Pain?

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INTRODUCTION

Exercise for low back pain (LBP) can be land- or water-based. It can involve isolated trunk muscle strengthening or cardiovascular conditioning. It can focus on hypermobile or hypomobile lumbar segments, address low back pain at different stages in its development, or have directional preference for flexion or extension movement. This manuscript will address different types of exercises and their roles in treating LBP.

THE SAFETY OF EXERCISE

Despite speculation that exercise increases disk degeneration and causes herniation due to torsional and impact loads on the spine, data consistently show otherwise. Over a 5-year period, Elfering and colleagues performed serial lumbar magnetic resonance imaging (MRI) on asymptomatic adults and found that lack of sports activities, rather than participation in them, predicted progression of disk degeneration.1 In a study of exercise patterns in 287 patients with herniated lumbar disks, Mundt and colleagues found no increased risk of disk herniation in the active group compared to age-matched nonactive controls.2 Randomized controlled trials of exercise for acute, subacute, or chronic LBP have also failed to show increased risk for back injury in exercise groups.3-7 However, these studies often limit exercise to one type and make comparison difficult by defining it in a variety of ways.

EXERCISE, NATURAL HISTORY, AND ACUTE LBP

“The art of medicine consists of amusing the patient while nature cures the disease.”—Voltaire

LBP, which is second only to the common cold as the most frequent cause for a primary care visit,8 has a benign natural history. Studies show that 40-50% of acute cases resolve in 1 week, and 85-90% do so in 6 to 12 weeks.9 All told, 90% resolve without physician interaction.10 However, long-term results have not been as positive.

Korff and colleagues found a significant amount of chronic LBP 1 and 2 years after an acute episode.11 Phillips and Grant showed that 62% of patients with acute episodes had one or more relapses during a 1-year follow-up, and 40% still had pain at 6 months.12 Carey and colleagues found that 95% of such patients had a functional recovery at 6 months, but 31% were not completely better.13 During 5 years of follow-up, Hestbaek and colleagues demonstrated that 33% of patients with LBP reported more than 30 days of pain during the baseline year, and 40% did so at years 1 and 5; at year 5, only 9% were pain free.14 Others have also reported that treatment was ineffective. Hart and Tulder and colleagues found no long-term differences in pain or function between conservative therapy and none at all in patients with acute LBP.15,16 A systematic review showed that advice as an
adjunct to exercise improved treatment outcomes for chronic lower back pain, but was no more effective than simple advice to stay active in patients with acute LBP. 

Many of the prospective, randomized trials indicating that exercise has no benefit in acute LBP patients, have methodological flaws. These include: no specific diagnosis; no corroborating physical examination or imaging findings; and use of the same treatment program for all patients. With conclusions based on nonspecific treatments for nonspecific diagnoses, it is not surprising that findings have been less than conclusive. This approach is akin to a cardiologist who gives every patient with “heart disease” one kind of medication or surgery. It is unlikely that all patients would benefit from such a narrow range of therapeutic options. The same is true for those with LBP.

Although most studies show no significant benefit from exercise, many emphasize its importance. Compared to patients who had passive treatment, those who followed advice to stay active had fewer physical therapy visits, lower cost of care, greater improvements in pain, and at 1-year follow-up, reduced likelihood of receiving prescription medications, MRIs, or epidural injections. These findings underscore the importance of including physical exercise in any treatment plan.

**SUBTYPES OF PATIENTS WITH LBP**

In 1937, Dr. Paul Williams introduced the concept of Williams Exercises. He based it on his assumption that LBP was due to increased lordosis causing unacceptable load on the posterior aspects of the intervertebral disk. He said, “Always sit, stand, walk and lie in a way that reduces the lumbar lordosis to a minimum.” His classic exercises, the first formal attempt to treat LBP in this way, included partial sit ups, knee to chest exercise, hamstring stretches, lunges or hip flexion stretches, seated flexion, and squats. He designed these exercises based on his claim that forcing the body to stand erect severely deformed the spine.

Robin McKenzie took another approach. Through observation, he developed a system of treatment based on mechanical assessment of patient movements. The evaluation process, which tests movements in different planes of motion, looks for symptoms of pain to either centralize or move from distal to proximal along a limb. The directional preference is used as the basis for therapy. For example, if the movement centralizes symptoms, and therefore reduces pain, it is used as the directional preference. This method applies to all phases of LBP—acute, subacute, or chronic.

McKenzie exercises have been misperceived as limited to spinal. In fact, patient response to a proper assessment dictates the direction of exercises. An extensive body of literature exists on patients treated with the McKenzie or mechanical assessment technique. Results show that the approach is useful in patients with most types of spinal pain.

Even without an assessment protocol, avoiding early morning flexion movements can lead to dramatic improvements in patients with nonspecific chronic LBP. Data suggest that flexion movements increase intradiscal pressure. Without motion to move nutrients in and out, intervertebral disks absorb fluid. Therefore, they are more “full” and susceptible to flexion movements early in the morning, before patients get out of bed.

In a crossover trial, Snook and colleagues compared early morning flexion avoidance with sham exercises in patients with chronic or recurrent back pain. The flexion avoidance group showed significant reductions in pain, medication use, and impairment, plus 18% fewer lost work days per month compared with the control group. Outcomes also indicated that 80% of all patients voluntarily continued to avoid early morning flexion after the study. A 3-year follow-up of the same patients demonstrated continued improvement in the flexion avoidance group, with a comparative decrease in pain days of 57%. The results of this study cast doubt on the efficacy of the Williams exercises. They also raise the issue of whether exercise can be optimized for specific kinds of back pain.

In a multicenter, randomized controlled trial, Long and colleagues studied LBP in subgroups (acute, subacute, chronic, axial, radicular, with or without neural findings) to evaluate the efficacy of “patient-specific” exercises in managing pain. Over 300 patients were assessed for directional preference (DP) or no DP. Those with a DP were randomized to directional exercises that “matched” their preferred DP, directly opposed it, or were “nondirectional.” Consistent with prior evidence, a standard mechanical assessment identified a large subgroup of patients (74%) with a DP. Exercises matching those DPs significantly and rapidly decreased pain and medication use and improved all other outcomes. Despite its short follow-up time of only 2 weeks, this study has important implications for clinicians.

In a randomized control trial in patients with 4 weeks to 6 months of subacute LBP, Klaber Moffet and colleagues compared a progressive exercise program based on a cognitive-behavioral approach (8 1-hour sessions) with usual primary care management. At 6 weeks, the intervention group improved marginally more than the control group on the disability questionnaire and reported less distressing pain. At 6 months and 1 year, it showed significantly greater improvement in the disability questionnaire score, and at 1 year, significantly greater improvement in the Aberdeen back pain scale. The intervention group reported only 378 days off work compared with 607 in the control group, and used fewer healthcare resources. The authors concluded that the exercise class was more clinically effective than traditional general practitioner management, regardless of patient preference. It was also cost effective.

The evidence for exercise in those with chronic LBP is probably stronger than for any other group of back pain patients. Alaranta and colleagues showed that a 3-week intensive exercise program reduced pain by 36% versus 20% in those who received passive treatment. Manniche and colleagues found that the greater the intensity of exercise, the greater the reduction in pain.
Conversely, Bendix and colleagues showed no difference between patients who received extensive exercise versus community treatments. Similarly, Hansen compared low-intensity exercise to conventional physical therapy and found no change in either group.

Numerous studies, however, have shown that exercise reduces disability from 8-50%. Kankaanpaa and colleagues compared the effects of active progressive treatment and passive therapy. After 12 weeks, patients in the active treatment group had less pain and self-experienced disability, as well as improved lumbar endurance. However, differences in lumbar endurance tended to diminish at the 1-year follow-up. In a meta-analysis of randomized control trials evaluating exercise therapy for LBP, Hayden and colleagues reported that patient-specific approaches and individually designed and supervised home exercise programs of longer duration and/or intensity were more effective than other treatment options.

**CORE EXERCISES – WHAT IS THEIR ROLE?**

The core muscles (Table 1) form a muscular corset around the lumbar spine. They support and stabilize it, act as a powerhouse for all limb movements, and serve as a foundation for local strength and balance. They contribute to spinal stability under various conditions by co-contracting, and are the most important muscles for maintaining spinal stability.

Stabilization exercises groove motor patterns that ensure sufficient stability for the task at hand. Kibler describes core stability as the ability to control the position and motion of the trunk over the pelvis, thereby allowing optimum production, transfer, and control of force and motion to the terminal segments in integrated athletic, kinetic chain activities. Core rehabilitation can be thought of as strengthening the multisegmented spinal column’s ability to maintain its center of gravity through multiple ranges of motion. This counteracts the effects of gravity and applied forces, and decreases torsion and shear on the spinal structures.

Many studies on LBP, especially chronic pain, have failed to show any benefit of core exercises compared with conventional physical therapy, manual therapy, or general exercise. Standaert and colleagues found strong evidence that lumbar stabilization exercise is no more effective than a less specific, general exercise program administered within an activating treatment structure.

However, O’Sullivan and colleagues showed that specific stabilizing exercises were more beneficial than a program of traditional, nonspecific exercise in chronic LBP patients diagnosed with spondylolisthesis or spondylolysis. The treatment group, which received 10 weeks of strengthening deep abdominal and multifidi muscles proximal to a pars defect, showed decreased pain and disability at 30-month follow-up. Fritz and colleagues found that lower back pain patients with lumbar hypomobility improved more from an intervention that included manipulation, while those with hypermobility were more likely to benefit from a stabilization program. Failure rates in the hypomobility group were 26% with manipulation versus 74.4% with stabilization. Respectively rates in the hypermobility group were 83.3% and 22.2% for manipulation and stabilization.

As mentioned earlier, it is unlikely that any one type of exercise will be effective for all kinds of LBP. Methodological problems with studies also make it difficult to draw conclusions. LBP has many etiologies and many confounding variables that make it very difficult for a single study to reach statistical significance, let alone clinical relevance. Any specific exercise program is more likely to work if it is performed on LBP patients who are classified into appropriate subgroups.

**EXERCISE PREVENTION FOR LBP**

In a meta-analysis, Bigos and colleagues found strong and consistent evidence that exercise has a significant impact on preventing symptoms and reducing back-pain related work loss. The authors reported positive results in seven out of eight trials evaluating exercise; three of them showed significant differences in work absence for subsequent LBP episodes.

However, most people in the United States avoid exercise—they either don’t like it or don’t want to do it. Fifty-nine percent of residents engage in moderate sports or recreational activities; 32% regularly participate in vigorous exercise; and only 15% report regular weight lifting. All too often, the high cost of inactivity becomes apparent after LBP is present. Thus, we need to ask ourselves whether the addition of exercise into our daily schedules is worth the effort to offset morbidity.

**CONCLUSION**

Exercise appears to do no harm and may even prevent LBP. All patients may receive some benefit from it, especially those with...
chronic LBP. Appropriate subgrouping may improve LBP, regardless of whether it's acute or chronic. It is clear that taking no action does not necessarily work very well for LBP.

REFERENCES


INTRODUCTION

The physical medicine physician is challenged to design exercise techniques to minimize pain and address the specific patient deficits. Each exercise must be fine-tuned to minimize joint loading, and create muscle-activity patterns that balance joint forces, equilibrate stress, ensure joint stability, and achieve the appropriate rehabilitation and training levels. Subtle adjustments in posture and muscle cues are made which the patient executes with precision. Now the question is: Have these objectives been optimized – has the balance been struck? The answer lies in a blend of clinical art and science. Over the last 25 years we have attempted to quantify exercise and the techniques of provocative testing and patient assessment, and to design tolerable exercises to address the deficits. This manuscript will provide some of our thoughts on how to arrive at the optimal answers.

I work at the interface between both clinical and basic sciences pertaining to normal function of the back, pathology and injury mechanics, patient assessment, therapeutic exercise and high-performance training. Interestingly, I am referred difficult patient cases from around the world (which is unusual as I am not a physician) and these cases include the failed backs, and the troubled backs of some of the best high-performance athletes. The reasons for referral are several: insufficient assessment was performed; the starting level of the therapy was incorrect; the progression of challenge was incorrect; and/or the therapy approach was incorrect. This could have been solved with an assessment to determine the tolerance and capacity of the individual, and then using this information to design the program beginning with corrective exercise. The following sections will help to create an algorithmic approach to this process.

In physical medicine, the first steps to evaluating a patient are determining the mechanically based etiology and the course of treatment. Curiously, the often heard statement “85% of low back pain is of unknown etiology” appears to have no scientific foundation, leads to frustration on the part of the clinician and the default diagnosis “nonspecific back pain”, which leads to despair on the part of the patient. Worse yet, it leads to patients being told that the pain is in their head, or that if left alone it will resolve in a few weeks.

Interestingly, it is well documented that those who have chronic, and/or recurrent episodes of disabling back pain, are different from those performing similar tasks who are symptom free. Here is where the common wisdom is false. This author and colleagues compared a group of workers performing similar tasks; 26 had chronic recurrent back pain episodes sufficient to miss work while 43 had no history of disabling back disorders. All were asymptomatic at the time of rather exhaustive testing. The 26 workers with “bad backs” did not have the weaker backs when measured, but rather had the stronger backs. When performing similar tasks the group with “bad backs” moved in a way to create more spine loading, which in turn strengthened their backs. It was concluded that because they overused their backs, it became the location of stress concentration. But when measured the group with “bad backs” had less torso muscle endurance than their pain-free colleagues.1 Generally, those with more motion in their backs have a greater risk of future back troubles.2,3

In contrast, poor hip mobility is linked to back pain.1 There is strong evidence that low back pain has a cause, that the cause can be determined and eliminated, and that appropriate therapy is both rehabilitating and prophylactic. The way people with painful backs move and load their tissues produces nonoptimal motion and
motor patterns that both cause, and resulting inappropriate joint mobility and stability. Provocative testing can identify the patterns that cause pain, provide clues to eliminate the cause, and establish the most efficacious therapeutic exercise approach. Changes and adjustments in therapeutic exercise technique can make the difference between rehabilitative success or failure.

**Tolerance and Capacity**

Determining the tolerance and capacity of each individual patient is paramount to ensure that a given therapy is matched to that patient. Each patient has a loading tolerance that, when exceeded, will cause pain and ultimately tissue damage. For example, a patient may tolerate a birddog extension posture, but not a superman extension over a gym ball which imposes twice the compressive load on the lumbar spine. An individual’s capacity is the cumulative work that he or she can perform before pain or troubles begin. For example, a patient who can only walk 20 meters before pain sets in has a low capacity. This person won’t benefit from therapeutic exercise that is performed three times per week; instead, he or she has a better chance with three sessions per day. Corrected walking in three short sessions per day, never exceeding the current tolerance and capacity, is an alternate approach to building capacity. Typically, patients will progress to one session per day as their pain-free capacity grows.

**Interpreting Patient Presentation and Finding Perturbed Patterns**

Elimination of the possible “red flag” conditions that could be associated with new back pain is a critically important first step. Then physical assessment usually consists of documenting the extent of motion (amount of flexion for example) along with some neural testing. How do these assist in designing prevention and therapy strategies? The answer is, they don’t.5

Geoff Maitland, the Australian physiotherapist, years ago promoted the concept of examining the patient and forming a working hypothesis to guide treatment, and project a prognosis (which was extremely helpful for cases involving litigation). The hypothesis was then tested and refined as rehabilitation progressed. Our approach, which incorporates a strong biomechanical foundation, and blends expertise from various biomedical/psychosocial disciplines, is very aligned with Maitland’s proposition. First, an initial impression is formed when first meeting the patient in the waiting room – their sitting posture, how they rise from the chair, their initial gait pattern, etc., are qualitatively assessed. Then a patient history is taken looking for possible injury mechanisms and perceived pain exacerbators and relievers. A key question to ask the patient is, “Do you have good and bad days – or better and worse days?” If the answer is yes, the doctor is assured that they can help this person. It is a matter of identifying those motion/motor patterns and loads that make the patient worse (and removing them) together with those that make them better (and assuring the therapy incorporated these tolerable postures, motions and loads). Observation continues during some basic motion patterns as the evaluation process proceeds delving further into the mechanics and nature of the symptoms. Then provocative tests are performed to either strengthen or weaken the hypothesis. Motion and motor patterns that are tolerated are identified. All information is used to formulate the plan for corrective exercise and the starting dosage of tolerable therapeutic exercise. The process concludes with functional screens and tests that were chosen based on information obtained in the preceding process; the assessment process is well documented in McGill.3 These results are used to substantiate some speculation as to the existence of perturbed motion and motor patterns and for considering exercise choices and rates of subsequent progression. No doubt you have heard the phrase “80% of back troubles are idiopathic” – the algorithm presented here including the provocative testing approach would make this notion obsolete and could be uttered only by one of very limited back expertise.

**Interpreting Patient Presentation**

To a working hypothesis, continue to reassess the hypothesis during the following assessment tasks:

1. Observe everything, starting with rising from the waiting room chair.

2. History – link injury mechanisms, pain mechanisms.

3. Perform provocative tests – which loads, postures and motions exacerbate, which relieve?

4. Perform functional screens and tests – are there perturbed postural, motion and motor patterns.

The important concept of the “degenerative cascade”, eloquently introduced by Kirkaldy-Willis6 some years ago, is another concept that results in heartache and injustice in too many compensation cases. Back troubles in many cases do not heal within 6-12 weeks, which is a common time statute for insurance benefits. I am referred too many cases for consultation where the patient has been accused of “bizarre” presentation, or is labeled as “noncompliant” or psychosocial because, most unfortunately, the degenerative cascade was not noted or considered. For example, disc annular damage is most often preceded by end-plate damage. Following annular damage, there is often a change in joint biomechanics which causes secondary facet overload, which presents a greater challenge to the therapist. Compounding this are the reports from other clinicians giving their opinion on the patient, and because the patient fails to “heal” within 3 months, they question the genuine motives of the patient. Some unfortunate souls are unjustly cutoff from benefits. No wonder such a patient displays psychosocial markers! This scenario can be avoided with knowledge of the injury mechanism and the subsequent degenerative cascade. Clinicians must stand firm in their knowledge that many spinal tissues do not heal within 3 months and the degenerative cascade accounts for lingering symptoms from one cascading tissue to the next for years. This helps them to be stronger advocates for their patients and their practice.

Many therapy approaches have the objectives of strengthening muscle and increasing spine range of motion. This is problematic7
since those who have more motion in their backs have a greater risk of having future back troubles. Strength may, or may not, help a particular individual. Interestingly, the differences between many “troubled backs” (the chronic back with recurrent episodes) and the backs of matched asymptomatic control subjects performing the same tasks, have been shown to be variables other than strength or mobility. Rather, deficits in motion and motor patterns have been documented as being more critical and therefore should be targets for therapy. For example, people with troubled backs use their backs more. Generally, they walk, sit, stand, and lift using mechanics that increase back loads. Many of them have stronger backs, but are less endurable than matched asymptomatic control subjects. They tend to have more motion in their backs and less motion and load in their hips. A common aberrant motor pattern known as “gluteal amnesia” may be both a common consequence of back troubles, as well as a probable cause. Optimal back exercise therapy results from the identification of these patients with perturbed patterns followed by specific corrective exercise – this precedes all other exercise therapy.

Examples of Some Provocative Tests That are Helpful

Provocative testing of motions, loads, and postures will identify those that exacerbate pain. If sitting is not tolerated, avoidance of flexion with a lumbar support may help ease pain together with designing work to eliminate prolonged flexion. Encoding the “hip hinge” movement pattern into daily activities can help to eliminate the cause of the pain. Specific exercises are designed to combat the cumulative stresses of sitting, together with exercises to correct any other perturbed motion/motor patterns. Thus if a patient has better and worse days you are guaranteed success by discovering the reasons.

I have illustrated many provocative tests based on motion, posture, and load, together with some corrective techniques in a DVD. For example, testing for compressive or shear load tolerance is easily performed in the office. Testing whether spine flexion or extension is a cause of pain, is also very productive as is testing whether neurological signs can be lessened through posture change, or whether nerve mobilizing approaches have a good chance for success in sciatic patients. Recognizing aberrant motion and motor patterns that load the known pain-producing structures is also straightforward with specific techniques, which are shown in Figure 5.

Figure 1 shows an example of provocative testing for compressive load tolerance. This posture-modulated tolerance provides powerful information to the clinician and can serve as a guide to avoid damaging/exacerbating activity, and it also helps to design appropriate therapy for the patient.

Testing for extension intolerance can begin by simply having the patient lie prone with the fists under the chin. Not only does this indicate tolerance (and often relief), but it also helps identify the posterior disc syndrome patient. Our tissue work has shown that those with posterior disc bulges, without substantial disc height loss, quite often respond well with this posture, as the hydraulic pressures assist to return the nucleus in the posterior annulus back to the nucleus. This does not happen in patients with substantial disc height loss, or when the disc damage includes circumferential rents where nucleus material has invaded the delaminated space between the annulus layers.

Similarly, it is worthwhile to test whether adverse neurologic signs, i.e., stronger reflexes, or decreased neurogenic pain, can be lessened by changes in posture. This kind of assessment also reveals whether nerve-mobilizing approaches have a good chance of success in sciatic or stenotic patients. Finally, specific techniques can help recognize aberrant motion and motor patterns that load the known pain-producing structures. Several of these techniques are shown in low back disorders. Instability catches observed as the patient moves through the neutral zone of spine motion are usually better indicators of instability and the generators of pain than assessments of absolute motion. Interestingly, muscular bracing patterns are usually found to eliminate the pain. When in a standing posture, for instance, or when walking, mild stiffening of the abdominal muscles will provide sufficient stability to get rid of the pain in the unstable, compression-tolerant back. Skilled clinical technique will better reveal mechanical causes of pain together with strategies to remove the pain.

The Art and Science of Designing Therapeutic Exercise:

Discussions of generic exercise for the back patient are not helpful and may even be harmful. Many Yoga and Pilates exercises may be appropriate for some, but may replicate the cause of trouble for others. The unstable back needs stability and probably mobility in the hips. The stiff back, not to be confused with a back splinted with muscle contraction, needs another approach. The older arthritic and stenotic back needs yet another therapeutic exercise approach. But matching the exercise program to the specific patient has changed the lives of many “failed backs”.

Figure 1  An example of provocative testing. The patient compresses the spine by grabbing the side edges of the seat and pulling down. When doing this with an upright back (a) the torso is stiffened with muscle activity. The test is then repeated in a slouched posture (b) discomfort in this position as compared to an upright back shows a lower tolerance when the spine is flexed (and a flexion intolerant patient).
Other considerations include exercise dosage: How often and how much? The answer lies in the tolerance and capacity of the patient. Those with extremely low tolerance must train with less intensity more often. For example, if the patient can only walk 10 steps without pain, then they will walk 6 steps every 30 minutes. A more rigorous session would ensure they break into pain. As tolerance increases, the steps will increase and slowly the interval between sessions will be lengthened. Optimal design of exercise dosage, and the length of the interval between sessions, will render superior results.

There has been much discussion about warm-up prior to exercise, and the order of the therapeutic exercise. Static stretching generally inhibits the neuromuscular system and should be very judiciously considered. Of course stretching to achieve joint and body awareness, or to address asymmetries in the lower extremities may be justified and in such a case it would be considered corrective. On the other hand, active flexibility, where the motions are conducted under control, with neural drive to the muscles, has been shown to be both facilitating of the neuromuscular system and helpful in re-patterning perturbed motor patterns.5 We have shown that the least stressful way to mobilize the back is to perform the cat-camel motion, only through the pain-free range of motion, while the patient is on their hands and knees. Viscosity is reduced with only a few repetition (no more than 10) as more repetition does not enhance this feature, but unnecessarily irritates tissues.11

Corrective and Rehabilitative Exercise

Rehabilitation is a staged process. My textbooks illustrate the many considerations and techniques to hone clinical skills at each stage and include the list below.

Stages of therapeutic exercise:

1. Corrective exercise: postures and motions
2. Build whole body and joint stability/mobility
3. Increase endurance

And for occupational/athletic clients:

4. Build strength
5. Develop speed, power/agility

Corrective Exercise: Postures and Motions

The first stage of designing the appropriate corrective exercise emanates from the identification of any perturbed motion and motor patterns. Every exercise is considered within the working diagnostic hypothesis in that the first time the exercise is performed it is considered a provocation test. If it is tolerated the patient can proceed. If it is not tolerated, the technique is reexamined and adjusted and/or a more tolerable variation is prescribed. Simple standing posture is corrected to eliminate extensor muscle contraction eliminating the need for muscle relaxants (Figure 2). An example of a motor pattern correction would be gluteal muscle activation retraining based primarily on the original work of ProfessorJanda has been honed in our own lab (Figure 3). This cannot be accomplished with traditional squat training.12 Chronic back pain tends to cause hip extension using the hamstrings, which leads to subsequent back extension using the spine extensors, creating unnecessary crushing loads. Gluteal muscle re-integration helps to unload the back. Another critical concept for this stage of exercise design is that technique "details" are important. It is not a matter of patient performing an exercise – it is a matter of the patient performing the exercise with perfection. Exercise form, subtle maneuvers to eliminate pain, pacing, duration, and other co-considerations are all extremely important.

Build Whole Body and Joint Stability

The next stage in the progressive algorithm is to groove patterns to ensure stability. Stability is considered at two levels - joint stability (in
Of course stability in the torso is accompanied by mobility at the hips and the interplay and correction is determined with assessment of the patient to move and handle load. Quantification of stability proves that these two objectives are fundamentally different and need two different exercise approaches. Our observation is that the two types of stability are often confused in the clinic. We are dismayed to observe many unstable spines given gym ball exercises as a standard treatment course—this often retards progress. True spine stability is achieved with “balanced” stiffening from the entire musculature including the rectus abdominis and the abdominal wall, quadratus lumborum, latissimus dorsi, and the back extensors of longissimus, iliocostalis and multifidus. Focusing on a single muscle generally does not enhance stability, but creates patterns that when quantified result in less stability. It is impossible to train muscles such as transverse abdominis or multifidus in isolation—a person cannot activate just these muscles. Do not perform abdominal hollowing techniques as it reduces the potential energy of the column causing it to fail at lower applied loads. Interestingly, a recent clinical trial compared the efficacy of many of the exercises that were quantified and published in the journal *Physical Therapy*, with the same exercises combined with specific transverse abdominis isolation (hollowing, etc.). Adding the specific transverse abdominis training reduced efficacy, whereas, the abdominal brace (contracting all abdominal muscles) enhanced stability. Target contraction levels for bracing and training techniques are described in McGill. Finally, some provocative tests, such as a shear test, will help reveal which classification of patient is best suited for a stabilization approach. Variations of our “Big 3” stabilization exercises have been quantified and selected for their ability to ensure sufficient spine stability and optimal motor patterns, they spare the spine of many injury mechanisms and pain exacerbators, and are designed to build muscle endurance (Figures 4,5,6). Then specific muscle group endurance is enhanced. Spine stability requires that the musculature be co-contracted for substantial durations, but at relatively low levels of contraction. This is an endurance and motor control challenge—not a strength challenge.

Technique corrections enable the dosage of these exercises to be increased without breaking the patient into pain (Figures 7,8).

A recent report documented these “expert” corrections. When performing the curl-up while breathing, “raking of the fascia” overlying the obliques, causes less rectus abdominis activity (from 34 to 17% maximum voluntary contraction [MVC] on average) and more activity in the internal oblique (36 to 50% MVC, p = .002) and latissimus dorsi (4 to 11% MVC, p = .004). Note also that the amount of spine flexion decreased from 9 to 2 degrees indicating a more neutral spine. Corrected technique during the side-bridge to eliminate spine twist can be obtained with a rolling action which emphasizes locking the ribcage to the pelvis. This correction significantly increased activity in both the obliques and latissimus dorsi (for example 18 to 35% MVC in latissimus when minimal torso twist was emphasized). Torso twisting was reduced from 11 to 4 degrees with corrected instruction. “Expert instruction” during the birddog, where the hand and foot “drew squares”, significantly increased activity in the left internal oblique and latissimus dorsi. The correction also resulted in a more neutral spine (spine flexion decreasing from 16 to 0 degrees with expert correction).
The next stage builds an endurance base. This is necessary to ensure that the patient is able to repeat perfect, joint sparing, motion and motor patterns for as long as necessary. The endurance progression begins by repeating short holds of postures. In this way tolerance is built without causing muscle pain or prolonged joint load. Each subsequent set is reduced in repetition number, an approach known as the Russian descending pyramid, ensuring impeccable exercise progressions. For this reason we have quantified exercises in this way to allow evidence-based decisions when planning optimal exercise progressions.

**INCREASE ENDURANCE**

For many patients wanting to accomplish tasks of daily living pain free, this evolution of exercise is sufficient. In the preceding progressions strength is enhanced as are specific patterns such as the ability to squat, push/pull, lunge etc. But strength is not specifically trained since this requires overload and elevated risk – this is reserved for performance training. Many people, whether they have athletic objectives, such as wanting to play golf, or have demanding occupations will fall into this category. On the other hand, many patients confuse health objectives, such asminimizing pain and developing joint sparing strategies, with performance objectives which require risk and compromise their progress when specific strength training is introduced too early. Many exercises typically prescribed to low back patients are done so without the clinician having knowledge of the spine load and associated muscle activation levels. For this reason we have quantified exercises in this way to allow evidence-based decisions when planning optimal exercise progressions.

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**CONCLUSION**

Clinicians can choose techniques to help make an exercise tolerable for a patient that includes muscle activation, movement and posture changes. The corollary is that failure to do so can make the same exercise painful. The evidence and techniques presented here may be used to assist clinical decisions regarding the starting exercise challenge, progression, corrective technique, and exercise selection. Further, studies of spine load clearly show that exercises that create torque challenge in the sagittal plane (flexion and extension) create the lowest load penalty on the spine. Frontal plane torque (lateral bending torque such as in a suitcase carry) is more expensive in terms of spine load. However, transverse plane torque (twisting torque) causes about four to five times more compression on the spine than an equivalent magnitude sagittal torque. Designing exercise to begin with sagittal loading first always produces superior results. As I stated at the outset I have told a more complete story in my books. This short manuscript simply cannot convey the complex approaches and objectives than training to fulfill rehabilitation objectives. Some of the techniques developed in our work with world class athletes are rather extensive and are better developed in my *Ultimate Back Fitness* textbook within the context of valid mechanisms and evidence. These include the progressions from establishing motor control patterns once the appropriate corrective exercise was performed, through to stability, endurance, strength, speed, power, and agility. A note is needed here – power development in the spine is usually very risky. Power is developed about the shoulders and hips to both increase performance and to minimize risk to the spine and related tissues.

However, corrective exercises continue throughout performance progressions allowing the patient/athlete to reach a much higher level of training and performance without pain. For example, in lifters focus is directed towards eliminating spine motion and facilitating more motion about the hips. Generally much more activation is enhanced in muscle like lattisimus dorsi through “bending of the bar” techniques. In golfers, the muscle pulse associated with hitting the long ball must occur when the spine is not deviated approximately at the time just prior to ball contact. This has spared some top golfers.
ponents necessary to be an elite clinician, but at least it may elevate awareness of some of the issues.

Acknowledgement: The many years of financial support that underwrote the series of works documented here are gratefully acknowledged the Natural Sciences and Research Council, Canada.

REFERENCES

The answer to the question about how to write an exercise prescription for low back pain is that really there is no one method or mechanism proven to be better than another. Despite this, I will do my best to walk through the steps I take each day with patients in coming to some kind of conclusion about what to do with this prevalent and often disabling condition that has no one proven exact method of treatment. So please recognize that this is just one physician’s approach and purely an opinion. Also, this opinion has not been vetted by the valuable process of peer review. Basically, this is the written form of how I make it through the day.

Low back pain (LBP) is a disorder that is prevalent, often disabling, and costly. In two National Health Surveys compiled between 1999 and 2005, one in two persons reported experiencing LBP once a year. Spine condition costs rose from 130.2 billion dollars in 1996 to 193.9 billion dollars in 2004. Further, between the years 2000 and 2004, earnings loss and indirect costs due to spine conditions were estimated at 22.4 billion dollars. No one treatment protocol has been found to address this overwhelming condition. Therapeutic exercise is considered one component of a treatment program. The prescription for exercise can vary and is dependent on the prescribing physician’s experience and the experience of the practitioner implementing the therapeutic exercise program. These experiences come in various forms including training background, type of practice, and years of experience. Further, the individual needs of the patient based on history, physical examination, and diagnostic testing should match the therapeutic exercise prescribed. The examiner needs to take into account the patient’s diagnosis, acuity occupation, sport, and exercise goals.

How to write a prescription is really a two-part question. First, what type of exercise would the patient most benefit from and second, how does one convey that recommendation in the form of a prescription. This manuscript will discuss the general categories of therapeutic exercise, give examples of when one might prescribe the intervention, and provide an outline of the components of a therapeutic exercise prescription.

Some of the confusion surrounding the topic of exercise and LBP comes from the fact that many studies do not specify the patient population being studied. Often studies will include patients of mixed acuity of symptoms, large age ranges, nonsimilar numbers of gender, mixed work-related injuries, and history of surgery(ies). Studying a nonspecific group can lead to variable outcomes. Further, studies have also included mixed-symptom presentations. Patients with LBP only may be included with patients with low back and leg pain.

Several research groups have focused on describing subgroups of patients of patients with LBP in order to better outline and measure treatment outcomes. Fritz and colleagues described history and...
clinical examination variables in patients with acute LBP (mean duration of pain 16.5 days) that could discriminate among treatment-based classification (TBC) groups. Subjects underwent an initial examination, completed self-report measures, and were classified for treatment by a physical therapist who had received university-level training with the TBC system. They recruited 131 participants with mean age 37.7 years, and 50.4% were female. Forty-five percent had a previous history of LBP; 52.7% had work-related LBP; and 40.5% had leg pain. Utilizing the TBC system, 38.8% of study participants were classified for specific exercise, 32.1% for mobilization, and 7.6% for traction intervention. A history of LBP, duration of symptoms, and present pain intensity best predicted the immobilization classification. Lower extremity pain, present pain intensity, and lack of lumbar flexion best predicted the specific exercise classification.

In a multicenter randomized controlled trial, another group utilizing the directional preference classification system studied LBP subgroups to evaluate different responses to contrasting exercise prescriptions. Three-hundred-twelve participants with acute, subacute, and chronic LBP and LBP with lower-extremity pain underwent a standardized assessment. Seventy-four percent (230) were classified into the directional preference group indicating they had improvement in pain after performing repeated lumbar flexion, extension, or side glide/rotation tests. These directional preference participants were randomized into one of three groups: (1) directional exercises “matching” their preferred direction; (2) exercises directionally “opposite” their directional preference; and (3) “nondirectional” exercises. The outcome measures included pain intensity, location, disability, medication use, degree of recovery, depression, and work interference. One third of both the opposite and non-directionally treated subjects withdrew within 2 weeks because of no improvement or worsening while no matched subjects withdrew. Exercises that matched participants’ directional preference significantly decreased pain and medication use as well as all other outcomes measured. This study speaks to the importance of treating specific subgroups of patients with LBP with exercise specific to their symptoms and response to maneuvers.

Utilizing another method of assessment and movement diagnosis system, VanDillen and colleagues published the evidence that specific clusters of tests of alignment and movement can be used to classify LBP into movement-system-related categories. In one study, 5 physical therapists examined 185 patients with LBP utilizing the standardized movement impairment based examination and assessed the effect on symptoms of modifying patient-preferred movements and alignments of the lumbar spine. Seven tests were designated as primary tests. Tests found to increase the patient’s symptoms were followed immediately by a secondary maneuver that facilitated the patient-preferred lumbar spine movement or the lumbar spine was positioned in a neutral position. Patients reported the effect of the secondary test on symptoms relative to their symptoms with the primary test. Eighty-three percent of the patients reported an increase in symptoms with one or more of the seven primary tests. Ninety-five percent who reported an increase in symptoms with at least one of the primary tests reported a decrease in symptoms with one or more of the seven secondary tests. The majority of patients reported a decrease in symptoms when the spinal movement or alignment was modified for six of the seven secondary tests. The authors concluded that modifying the symptom-provoking movements and alignments of the spine during symptom testing resulted in a decrease in symptoms for the majority of patients. Further, these movement tests that provoke and relieve symptoms can be utilized to direct a therapeutic exercise program.

Though a variety of therapeutic treatment models have been shown to be beneficial in evaluation and treatment, it is apparent that an individualized approach is important. Descarreaux and colleagues studied patients with sub-acute and chronic LBP. One group of patients was given an individualized and specific therapeutic home exercise program based on the patient’s examination and were compared to a group given a nonspecific home exercise program. Both of the groups showed some improvements in muscle strength and flexibility, but only the specific exercise group members had a significant reduction in pain and disability.

In summary, no one method is 100 percent successful in describing all subgroups of LBP and hence the debate between therapeutic models will continue. From just the few publications of the thousands written on this topic, it is apparent that specifically describing a population that an intervention is applied to help is key in determining the intervention’s value with regards to patient benefit and outcome.

**Therapeutic Exercise Systems and Methods**

There are many therapeutic exercise systems and methods of treatment. Some have been validated in the literature outlining reliability in the evaluation of the patient and improved treatment outcomes. General classifications this author uses to group the systems in a general fashion will be discussed. Grouping them assists in working through the decision-making process and assists in determining which type of treatment(s) the patient might benefit from most.

Systems that focus primarily on stabilization and strength include core strengthening and stabilization, (McGill) and resistance training. McGill presents the biomechanical basis that supports the benefit of strengthening the trunk muscles to enhance “stability” of the lumbar spine.

The benefits of resistance training have also been shown for patients with LBP. Leggett and colleagues evaluated 400 patients with chronic back pain. They investigated the efficacy of a standardized treatment method using isolated lumbar strength testing and strengthening exercises based on progressive protocols using specific equipment implemented a two different treatment sites. Patient improvement during the course of the program and at 1-year follow-up was similar at the two centers. Patients at both sites showed improvement in short form-36 scores, self-appraisal of improvement, and reuse of healthcare services. The authors concluded that standardized protocols using specific strength and measurement equipment at multiple sites were achievable and reproducible.
The directional preference system proposed by McKenzie provides a system of both evaluation and treatment. This method utilizes a specific set of maneuvers that, depending on the patient’s response to pain improvement, aids in subgrouping them into the following: postural syndrome, dysfunctional syndrome, and derangement syndrome. This subgrouping then directs the specific treatment intervention. Specifically, a directional preference is determined. This is an immediate, lasting improvement in pain from performing repeated lumbar flexion, extension, or side glide/rotation tests. This directional preference is then the central focus of the exercises implemented for the patient to perform independently.

Another method is the treatment-based classification system proposed and validated by De Litto. Like the McKenzie method, this system implements a standardized examination that subgroups patients by the methods in which their symptoms are reduced or eliminated. Essentially, the way they can be most successfully treated is how they are grouped. The major groupings include specific exercise, mobilization, immobilization, and traction. Further subgroupings in the specific exercise group include flexion, extension, and lateral shift syndromes. The mobilization group has lumbar and sacroiliac joint mobilization subgroups. The traction group has a traction syndrome and lateral shift syndrome subgroups. Again, each subgrouping directs specific treatment intervention. In the treatment-based classification system some of the treatment is applied by the specialists (i.e., mechanical traction) while some are directed by the specialist for the patient to perform independently.

The movement-based system of treatment proposed by Sahrmann involves a complex system of evaluation of movement in weight-bearing and non-weight-bearing positions to arrive at a movement-based diagnosis. The diagnosis then characterizes the subgroups for which treatment is directed. Movements the patient performs that reduce symptoms may initially be assisted by the specialist with the goal of the patient to perform them independently. The movement impairments associated with activities of daily living are also addressed. Tactile stimulation and taping might be used to assist with proprioceptive feedback to assist in correcting the movement impairments.

Manual medicine is another form of therapeutic treatment that can include exercise. There are a variety of types of manual medicine with a variety of origins. Osteopathic medicine has its musculoskeletal examination roots in manual medicine, as does chiropractic medicine. The theories behind them and indications for treatment differ between the two disciplines, but some similarities exist. Manual medicine includes joint mobilization techniques that physical therapists also utilize. In general, a joint restriction is assessed by one of these specialty disciplines. The treating specialist positions the patient in an optimum position and applies a passive force to the joint in an attempt to facilitate optimal joint movement. In some instances, the patient can be taught the mobilization techniques to perform independently. Strengthening and flexibility exercises may be taught to facilitate maintenance of the appropriate joint position after mobilization has been performed.

Modalities

This manuscript intentionally does not focus on modalities. Modalities can be beneficial adjuncts to therapeutic exercise, and should be utilized as a treatment that assists in modifying symptoms, but should not be seen as a stand-alone treatment. Often, the patient can be taught to use modalities independently before and after therapeutic exercise to modify symptoms. For acute pain or acute exacerbation of pain in the setting of a chronic condition, ice can be helpful in reducing inflammation and edema. For conditions involving a chronic condition where bringing blood to the region would be of benefit, heat can be useful. Though not absolute, in general neurogenic pain typically worsens with heat and may be modified with ice. Neither should be applied for more than 20 minutes at a time. Another treatment modality that historically has been utilized to reduce LBP and can be administered by a physical therapist is a transcutaneous electrical nerve stimulation (TENS) unit. Naslund and colleagues reviewed the literature regarding the use of TENS for musculoskeletal pain and found no overwhelming evidence of its benefit in this population. They did find evidence of its benefit for dysmenorrhea, angina, and acute post-operative pain. Despite this, a trial of TENS may be of benefit particularly in patients who are intolerant or unable to take medications to modify pain.

COMPONENTS OF THE EXERCISE PRESCRIPTION

Again, there is no right or wrong way to write an exercise prescription. The following is just one example that can be modified many ways.

Diagnosis

When writing a diagnosis for exercise prescription, it works best that the physician knows the background of the intended recipient. Unfortunately, this is not always possible. Patients who live a distance from the practitioner’s practice location, or insurance restrictions that allow patients only to be treated in certain facilities, can preclude a referral to a practice where the physician has a working relationship with other practitioners. Writing both the clinical and structural diagnosis for the physical therapist can eliminate confusion. Including the structural diagnosis gives the additional information to the therapist regarding the patient’s condition and also makes them aware of information that has been discussed with the patient. An example of diagnoses would be:

- **Clinical diagnosis:** LBP with right lower-extremity pain with positive dural tension in an S1 distribution.

- **Structural diagnosis:** L5 - S1 posterior lateral nucleus pulposus protrusion.

Precautions

Any medical precautions that the physical therapist should be made aware of should be listed on the prescription under precautions. These might include cardiac precautions, diabetes, cancer, and pregnancy. If a fracture is involved, weight-bearing status should be
listed as well. Further, restrictions/precautions regarding the lumbar spine should be included here. An example would be to avoid end-range flexion and lifting greater than 10 pounds in a patient with an acute vertebral compression fracture.

**Intervention and Education**

This section of the prescription lends itself well to a template. The content will vary greatly dependent on the patient and diagnosis. Recommendations for specific muscle flexibility and strengthening can be outlined as well as recommendations for educational instruction regarding posture, ergonomics, and sports, exercise, or work specific activity modifications. Utilization of taping to facilitate proprioceptive feedback and neuromobilization to aid in pain reduction can be added. The uses of modalities are also recommended in this section of the prescription. Instruction in a home exercise program should always be included. The number of visits can be listed in several forms. Putting an endpoint to the sessions is one way to insure that the physician gets appropriate written progress reports, which is important in order to justify further treatment to third party payers and confirms that no further diagnostic testing is needed. If the patient is benefiting from therapy, further goals can be set and the prescription for more visits can then be extended. Without appropriate interval documentation, the patient might utilize all of the allowable therapy sessions without improvement.

**Follow-up**

The prescription should also contain the physician’s contact information to facilitate communication and accessibility. Open communication between physical therapist and physician improves problem solving and reinforces the importance of a team approach to facilitate care.

**CHOOSING WHAT WILL BENEFIT THE PATIENT**

The real root of the question of how to write a therapeutic exercise prescription is really one of summarizing information and tailoring the prescription to the needs of the individual. This is never the answer physicians or patients want to hear. Everyone wants the diagram of “the” three exercises that will “fix” the pain. However, if all LBP would respond to three exercises, then the disorder would easily be resolved, impairment and disability minimized, and costs for spine care would be minimal. For the physician trying to make therapeutic exercise recommendations to the patient with LBP, he or she must assess the story the patient tells about the origin of pain, the physical examination, and the diagnostic testing results. Further, the physician needs to direct questions regarding the patient’s belief system and behavioral patterns to best tailor the prescription. Examples of the latter include patients who have tried physical therapy and experienced pain and may not be accepting of a therapeutic exercise prescription. Patients who demonstrate fear avoidance behavior will require further education by the physician to engage them in the benefits of therapeutic exercise and to recommend an appropriate therapeutic exercise plan.2

Which method of therapeutic exercise to prescribe is also dependent on the background and training of the physical therapists in the community where the patient will be treated. Therapist accessibility and experience often have a lot to do with the kind of treatment the patient receives. This can be a mismatch with what the patient needs and hence treatment recommendation and outcomes are variable.

Despite all of these confounding factors, the following is an attempt to give a general outline regarding how to write a therapeutic exercise prescription.

**Case**

A 35-year-old electrician and weekend warrior basketball player presents with LBP and right lower-extremity pain for 8 weeks. He complains of parasthesias into the dorsum of the right foot. He denies weakness, bowel or bladder incontinence, or changes in gait. His pain worsens with coughing, sitting, and lumbar flexion. He gets relief with lying supine with the hips and knees flexed, ice, and ibuprophen. He has not missed work, but pain worsens throughout the day and he has not played basketball because of the pain. His primary care physician ordered X-rays which were interpreted as “normal” and magnetic resonance imaging of the lumbar spine shows a posteriolateral disc protrusion at L4 - L5. His physical examination reveals normal muscle stretch reflexes, decreased pin prick sensation at the tip of the right great toe, and gluteus medius strength reduced. In the standing position, he demonstrated a right lumbar shift. He has pain with lumbar flexion and gets relief with lumbar extension. Side bending right provokes pain. Pain into the leg is also provoked with supine straight leg raise and slump sit test. An example of an exercise prescription is shown in Table 1.

This prescription is eclectic and incorporates several different therapy models into one prescription. Another prescription might incorporate only one model. At this time, the literature supports that both are beneficial, but neither an absolute right or wrong. As previously discussed here, there is good evidence that specificity of exercise is valuable1,2 and further specifying the subgroups of like patients being treated is not only advantageous, but necessary in order to compare like groups of patients and appropriately report treatment outcomes.2,3

**SUMMARY**

With the current evidence, there is no one therapeutic exercise that resolves all LBP. There is a growing body of literature that supports the benefit of therapeutic exercise, that specificity of exercise matters, and that classifying LBP patients into subgroups are all important factors in facilitating patient engagement in the therapeutic exercise process and improve outcomes. Choosing what will be most beneficial for the patient in the examination room is multifactorial. Factors to assimilate include the patient’s history, physical examination, belief system, and objective testing. Combining this information with what expertise is available to the patient in his or her community is one more example of how healthcare remains an art as well as a science.
Table 1 Example of an exercise prescription

<table>
<thead>
<tr>
<th>Physical Therapy Referral</th>
<th>Lower back pain and right lower extremity pain with positive dural tension in an L5 distribution consistent with radiculopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Diagnosis</td>
<td>L4 - L5 posterolateral disc protrusion</td>
</tr>
<tr>
<td>Structural Diagnosis</td>
<td></td>
</tr>
<tr>
<td>Precautions</td>
<td>Initially avoid flexion but progress to functional activities as pain allows</td>
</tr>
</tbody>
</table>

Treatment Recommendations

1. Directional preference exercise and education to initially promote pain reduction.
2. Education in self-correction of lumbar shift.
3. Neuromobilization as pain allows and direct patient in an independent program.
4. Progress to lumbar stabilization with specific attention to core muscles.
5. As pain centralizes and intensity decreases, progress to functional activities and adjust posture and ergonomics as possible.
6. Educate and provide exercise to facilitate appropriate movement patterns.
7. Assess sport-specific activities in all planes of motion and add exercise and technique changes as needed.
8. Ice as needed for symptom modification.
9. Review the patient's current aerobic and resistance exercise routine and modify and/or enhance as indicated.

Number of visits: 6-8 sessions

Please forward assessments and treatment plans to (phone and fax number)

REFERENCES

INTRODUCTION

Sarcopenia is defined as age-associated reduction in muscle mass to less than two standard deviations below age-matched norms, usually measured as lean body mass (LBM) or fat-free mass (FFM) using dual energy X-ray absorptiometry (DEXA) scanning. The prevalence of sarcopenia is about 10% in adults over the age of 70 and 20% in those over the age of 80. The accompanying muscle weakness of sarcopenia increases the risk of falls and functional impairments (i.e., activities of daily living) that can compromise personal independence.

The annual cost of sarcopenia to the U.S. healthcare system is an estimated $18 billion. A multifactorial condition, sarcopenia involves apoptosis, motor unit loss, oxidative stress, alterations in protein turnover, inflammation, hormonal dysregulation, disuse, and mitochondrial dysfunction (Table 1). In addition to loss of strength with aging, aerobic capacity also declines due to lower cardiac output (central factor) and a reduction in mitochondrial capacity (peripheral factor).

Sequela from the loss of strength and function make sarcopenia an important condition to address. Reduced knee extension and leg strength are associated with a higher risk of falls in both community dwelling and nursing home residents over the age of 65. Leg muscle weakness results in slower walking speed and a decline in functional capacities, e.g., the ability to climb stairs and rise from a chair. Studies show an inverse relationship between leg strength and the prevalence of falls and fractures. Countermeasures to increase strength and decrease the prevalence of sarcopenia will have a beneficial impact on society.

This manuscript will focus on the role of the mitochondria and oxidative stress as modulators of aging-associated sarcopenia. It will also review how resistance (RES) and endurance (END) exercise training counteract the effects of aging.

Table 1 Cellular causes of sarcopenia

<table>
<thead>
<tr>
<th>Cause</th>
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<tbody>
<tr>
<td>Oxidative stress</td>
</tr>
<tr>
<td>Mitochondrial dysfunction</td>
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<tr>
<td>Lower sex hormone concentration</td>
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<tr>
<td>Apoptosis</td>
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<tr>
<td>Alpha motor neuron loss</td>
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<tr>
<td>Reduced protein synthetic rate</td>
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<tr>
<td>Accumulation of aging pigments including advanced glycosylation end products and lipofuscin</td>
</tr>
<tr>
<td>Telomere shortening</td>
</tr>
<tr>
<td>Alterations in protein degradation</td>
</tr>
<tr>
<td>(increased myofibrillar)</td>
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<tr>
<td>(decrease in other proteins)</td>
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EFFECT OF AGING ON SKELETAL MUSCLE

Changes in Muscle Mass and Strength

Aging is associated with reduced skeletal muscle mass and an infiltration with intramyocellular lipid and connective tissue.30,32 FFM is maintained until the sixth decade of life and then declines.75,76,99,91 The resulting loss of muscle mass is associated with a progressive decline in strength.32 One study found that the isometric torque of the knee extensors (-44%) and elbow flexors (-32%) were both lower in 69-year-old men compared to those who were 28 years old.58 Muscle power (strength per unit time) decreases even more rapidly than peak strength with aging, and this reduction is also associated with impairments in physical capacity and function.70

Data show that age-associated decline in muscle strength is directly due to a loss of skeletal muscle mass.23,32,45,57 A longitudinal study of men 65 to 77 years of age found that reduction in cross-sectional muscle area over 12 years accounted for most (90%) of a 20-30% of men 65 to 77 years of age found that reduction in cross-sectional area over 12 years accounted for most (90%) of a 20-30% decrease in muscle mass.23,32,45,57 The reduction in muscle mass is associated with a decrease in muscle power (strength per unit time) decreases even more rapidly than peak strength with aging, and this reduction is also associated with impairments in physical capacity and function.70

In contrast, data also demonstrate that age-related decline in strength is independent of muscle mass loss, suggesting that muscle quality also declines with age.74 An increase in glycation-related collagen cross-linking of proteins in skeletal muscle from older adults may be one intrinsic factor that could attenuate contractile force independent of muscle mass. Similarly, increases in other age-associated pigments, such as lipofuscin, are another characteristic feature of the aging process.51

Aging of skeletal muscle may disproportionately affect type II (fast-twitch) muscle fibers. Some studies report smaller type II muscle fibers,2,18,42,58,63 while others suggest a decreased proportion of them.53,63 There may be a gender difference in fiber type loss, with older women, but not men, showing smaller type IIa fibers and lower myosin heavy chain IIa composition compared to younger adults.99 Together, these findings indicate that the decrease in whole muscle strength and mass may be due to a more selective loss of type II fiber size and number.

The etiology of the type II fiber loss is unclear. However, older adults (60 to 80 years) have approximately 50% of the motor unit number estimates (MUNE) in biceps brachii compared to those who are younger (20 to 40 years).23 The reduction in MUNEs may explain the decrease in the total number of type II muscle fibers in an entire muscle in older adults.69,68

Changes in Protein Turnover

At the protein turnover level, sarcopenia occurs when there is a negative balance between the rates of muscle protein synthesis and muscle protein breakdown. The rate of mixed muscle protein synthesis is lower in 60-70-year-old men and women compared to those who are 20 to 32 years old.112 More specifically, the myofibrillar protein fractional synthetic rate is 30% less in 60-70-year-old men compared to men < 35 years of age,104 and the age-related reduction in muscle synthetic rate is associated with a decline in fast myosin isoform messenger ribonucleic acid (mRNA) content.106

Studies report a positive correlation between knee extension strength and muscle mass and the rate of myosin protein synthesis in older adults.4 In addition, the rate of mitochondrial protein synthesis and electron transport chain (ETC) activity show parallel declines with age,86 with no changes in the rate of sarcoplasmic protein synthesis.4 Taken together, these outcomes suggest that the synthetic rates of myofibrillar and mitochondrial proteins are lower in older adults, and that these changes are associated with functional deficits seen with aging.81

Studies using whole body proteolysis or urinary 3-methylhistidine excretion (an indirect measure of myofibrillar proteolysis) measurements do not show an aging-associated increase with respect to muscle protein breakdown.109,112 One report found that basal, but not acute exercise-induced 3-methylhistidine concentrations, were higher in skeletal muscle microdialysate from older men compared to younger ones.100 In contrast, other data show an accumulation of damaged proteins related to an increase in protein half-life and lower ubiquitin-proteosome activity.39

The story is even more complex and may be protein-specific. Proteomic studies in rat skeletal muscle show lower overall abundance of some proteins, including creatine kinase, myosin light chain-3, and tropomyosin, with higher levels of myosin light chain-1, aconitase, and adenylate kinase.76 The conflicting myosin light chain findings76 and mixed results from earlier reports indicate that whole muscle measurements of synthesis and breakdown are confounded by protein specific turnover rates that may be differentially altered by the aging process.

Mitochondrial Dysfunction and the Link With Sarcopenia and Apoptosis

Several studies demonstrate lower skeletal muscle mitochondrial enzyme activity with aging in humans.18,86 The cause is likely to be multifactorial, however, several studies using human skeletal muscle have identified a transcriptional profile for downregulation of genes involved in mitochondrial function (Figure 1).35,72 The latter finding is seen in a variety of species, including worms, flies, and mammals. Recent data suggest that many of the genes/proteins/pathways implicated in aging of worms and flies have significant homology to humans.5

Our studies, and those of others, have found an age-associated accumulation of mitochondrial deoxyribonucleic acid (mtDNA) deletions in human skeletal muscle (Figure 2).50,78 Animal studies indicate that the accumulation of mtDNA deletions with aging is
highest in type I fibers, likely due to their higher mitochondrial volume.80 Given the few introns and lack of protective histones in mtDNA versus nuclear DNA (nDNA), there is a higher propensity for the stochastic accumulation of oxidative damage-mediated DNA mutations in mitochondrial DNA compared to nDNA.111

Although currently controversial,61,102 some suggest that the progressive accumulation of mtDNA mutations occurs from a “vicious cycle” in which free radicals generated by the ETC further induce mtDNA mutations. These, in turn, alter ETC proteins and increase generation of reactive oxygen species. Data show an association in which mtDNA mutations are the highest in cytochrome c oxidase (COX) negative muscle fibers.60,65,78 More atrophic muscle fibers in rats and nonhuman primates show a reduction in COX activity and an increase in mtDNA deletions; this is a particularly relevant observation.1,65

Strong support for the involvement of mitochondrial dysfunction in the aging process comes from the polymerase gamma mutator mouse model. Polymerase gamma is a nuclear-encoded mtDNA polymerase (PolG) that is essential for mtDNA replication and mitochondrial biogenesis.61,7,56,95 PolG mice (C57Bl/6J, PolgD257A/D257A) express a mutant form of PolG that lacks proofreading function due to a critical aspartate to alanine residue substitution in a conserved exonuclease domain.101 PolG mice demonstrate elevated mtDNA somatic mutations frequencies in many tissues, including muscle and brain.103 The accumulation of mtDNA point mutations results in mitochondrial respiratory chain dysfunction. This is indicated by decreased oxygen consumption and mitochondrial enzyme activity, and multisystem failure consistent with premature aging.61,62 Specifically, these mutator mice present an accelerated aging phenotype that includes muscular atrophy (sarcopenia), kyphosis, osteopenia, alopecia, loss of hair pigment and hearing, cataracts, cardiomyopathy, and reduced body weight. PolG mice also have a dramatically reduced lifespan, with a median survival of < 12 months compared to > 2 years in wild-type mice.101 Sarcopenia may also be related to myonuclear apoptosis with the subsequent loss of the myonuclear domain under control of the lost nuclei. Mitochondria play an important role in the activation of apoptosis through the release of cytochrome c, which interacts with apoptotic peptidase activating factor 1 (Apaf-1) and caspase-9 to form the apoptosome. They also activate downstream effector caspases, including caspase-3. Activation of apoptosis by the mitochondrial pathway involves the opening of the mitochondrial permeability transition (mega-pore), a process that is potentiated by free radicals.91

Data show a higher abundance of a number of apoptotic-related transcripts, including caspases 3,8,9 and apoptosis inducing factor, in skeletal muscle from old rats compared to young ones.3 DNA fragmentation in 24 month old rat gastrocnemius muscle is increased compared to that seen in 6 month old rats.22
Aging is associated with an increase in mitochondrial cytochrome c and endonuclease G release.\textsuperscript{13} Skeletal muscle from older rats and mice show a p53-associated activation of apoptotic pathways.\textsuperscript{94,25} The PolG mutator mouse has a large increase in mtDNA point mutations\textsuperscript{102} associated with an increase in cleaved caspase-3 in skeletal muscle.\textsuperscript{61}

\textbf{AGING AND RESISTANCE EXERCISE}

\textbf{Effects on Muscle Mass and Function}

A number of investigations show that RES exercise training leads to muscle hypertrophy and higher rates of muscle protein synthesis in middle age, older age, and physically frail older adults.\textsuperscript{10,15,27,29,31,71,97,113} Data suggest that 12 weeks of whole body RES exercise training can lead to an increase in type II muscle fiber area in men aged 64 to 86\textsuperscript{15} and 65 to 72.\textsuperscript{10,31} Our group reported higher type I and IIx muscle fiber areas following 4 months of RES exercise training in older men and women.\textsuperscript{9} In a 2-year study of RES exercise training, McCartney and colleagues reported an increase in leg press (32\%) and military press (90\%) one repetition maximum (1RM) strength as well as knee extensor muscle cross-sectional area (9\%) in 60- to 80-year-old men and women.\textsuperscript{71}

Masters athletes (69 ± 1 years) who performed RES exercise training had muscle strength that was similar, and in some movements higher, than young, sedentary men. This indicates that lifelong RES exercise may be protective against age-associated strength loss.\textsuperscript{58} Our data show an overall increase in strength after a few months of RES exercise training. This outcome is consistent with findings from other studies.\textsuperscript{9}

In addition to increases in muscle hypertrophy as the mechanism behind the increases in strength seen with RES exercise training, there is also evidence of a significant neural component.\textsuperscript{28,29,52,71} A 2-year study found that the increase in leg press (32\%) and military press (90\%) strength was much greater after RES exercise training than the corresponding increase in thigh cross-sectional area of only 9\% seen in older men and women.\textsuperscript{28,29,52,71} Part of the neural adaptation could be due to degeneration of the neuromuscular junction with aging and loss of motor units.\textsuperscript{23} Neural adaptations are an early and commonly seen component of strength increases during RES exercise training.\textsuperscript{88} In addition to muscle hypertrophy and neural changes, there are also increases in muscle quality, a variable measured by Tracey and colleagues with functional testing in 65 to 75 year old men.\textsuperscript{97}

Data show that even in older adults (80 to 86 years), the increase in strength and size of single fibers following RES exercise training is trivial compared to the increase in whole muscle strength, suggesting an increase in neural activation.\textsuperscript{90} However, single-fiber experiments report an increase in muscle fiber area, strength, and contractile strength/power for older men following RES exercise training, with no effect in older women.\textsuperscript{96}

The functional benefits of RES exercise training have been evaluated in physically frail nursing home residents (72 to 98 years old). Data show gains in muscle strength (113\%), gait velocity (12\%), stair climbing power (28\%), spontaneous physical activity, and thigh muscle cross-sectional area (2.7\%).\textsuperscript{29} These outcomes are in line with our group’s findings of consistent functional capacity improvements following both 4-9 and 6-month supervised RES exercise training programs. Increased muscle function that improves performance of activities of daily living reduces the burden of illness associated with weakness and immobility, and thus, has a beneficial impact on healthcare costs.\textsuperscript{29}

In contrast to little or no effect of RES exercise training on mitochondrial capacity in young adults, our recent data show that RES exercise training in older adults leads to improvements in skeletal muscle mitochondrial function;\textsuperscript{28,79,72} for example, increases in skeletal muscle COX enzyme activity as well as citrate synthase total protein content after 4 months of training.\textsuperscript{78,79} Safdar and colleagues also found that 6 months of RES exercise training reduced mtDNA deletions in skeletal muscle from older men and women (Safdar, A., et al, manuscript in preparation, 2009) and “reversed” the transcriptome signature of aging.\textsuperscript{72}

RES exercise training improves mitochondrial function and antioxidant defenses. It reduces whole body and muscle markers of oxidative stress in older adults, possibly due to an increase in antioxidant defense enzymes, such as catalase and manganese superoxide dismutase.\textsuperscript{78,79} A potential mechanism of action might be recruitment of satellite cells that can fuse with the mature muscle and “dilute” the older dysfunctional mitochondria through a process called “mtDNA shifting.”\textsuperscript{93} In patients with sporadic mitochondrial DNA mutations (deletions), the proportion of mutations in the mature muscle is much higher than it is in the satellite cells (approximately 3-4 % of myonuclei).\textsuperscript{16}

Data show that activation of the satellite cells through direct trauma or exercise diluted the mutational burden in the mature muscle when the satellite cells differentiated and fused,\textsuperscript{16} thereby lowering the proportion of mutated to wild-type genomes.\textsuperscript{29} Some studies suggest that the total number of satellite cells are lower in older adult muscle,\textsuperscript{55} yet they still retain the ability to activate and regenerate damaged muscle.\textsuperscript{19}

In contrast, other research indicates that several properties of aged satellite cells are altered, including antioxidant defenses.\textsuperscript{34} Following an acute bout of eccentrically biased resistance exercise, the number of activated satellite cells in older adults increased, but the gain was approximately 33\% that of younger adults.\textsuperscript{24}

Our recent findings show that mtDNA deletions, lower mitochondrial enzyme activity, and higher oxidative stress seen in the muscle of older adults (compared to younger ones) are not apparent in a primary myoblast culture (Safdar, A., et al, manuscript in preparation, 2009). Together, these data suggest that RES exercise training in older adults is associated with activation and recruitment of satellite cells into the mature muscle in a form of mtDNA gene shifting.\textsuperscript{16,9}
This phenomenon may be explained by the fact that satellite cells remain quiescent and relatively undamaged from lifelong exposure to free radicals derived from mitochondrial respiration, and 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**

Several longitudinal studies report increased maximal aerobic capacity (VO2max) after END exercise training in older adults. These improvements are likely to be of major benefit. Data show that men and women who run in middle age have a 50% reduction in mortality over a 21-year period and a significantly lower rate of cancer, and neurological and cardiovascular disease. Given that these three disorders are major contributors to hospitalizations and healthcare costs, aerobic activities are likely to play a key role in public health efforts to promote healthy lifestyle choices.

At the skeletal muscle level, END exercise training increases muscle capillarization, mitochondrial function, and myosin heavy chain I mRNA and protein content. Masters END exercise athletes do not show the expected age-related decline in mitochondrial function, and their decline in aerobic capacity is only 50% of that in age-matched sedentary individuals. Significant declines in insulin sensitivity associated with aging are also significantly improved by END exercise training.

In older adults, END exercise training is associated with reductions in both abdominal adipose tissue and dyslipidemia. It also decreases blood pressure more consistently than RES exercise training. Given that long-term END exercise does not usually lead to an increase in muscle mass or strength over that seen in sedentary age-matched controls, older adults may gain the greatest benefit by combining both END and RES exercise training to combat sarcopenia and several of the disorders associated with mitochondrial dysfunction.

**SUMMARY**

Aging is associated with reductions in skeletal muscle mass, function, and endurance that can lead to limitations in activities of daily living. Impaired functional capacity can increase the risk of disability (e.g., falls leading to fractures) and institutionalization, both of which increase healthcare costs. The progressive loss of muscle mass (sarcopenia) is multifactorial, but is associated with oxidative stress, mitochondrial dysfunction, inflammation, and apoptosis. Whether or not mitochondrial dysfunction and oxidative stress are directly linked, both are improved after RES or END exercise.

RES exercise improves muscle mass and function in older adults. This is likely due to both intrinsic improvements in muscle structure and function as well enhanced neural activation. END exercise is associated with improvements in aerobic capacity and mitochondrial function, with long-term benefits in decreased death rate, cardiovascular risks, cancer, and neurological disorders. RES exercise training delivers a “spill over” effect, adding gains in strength to the increased mitochondrial capacity seen in END exercise training.

RES and/or END exercise training in older adults can reduce morbidity and mortality by increasing muscle mass, strength, and mitochondrial capacity. A Cochrane review listed “muscle strengthening” (RES exercise training) as the main intervention associated with a reduction in risk of falls in older adults (3 trials, N = 566, relative risk = 0.80). This outcome was due in part to an improvement in balance.

Several studies in animals and humans show that habitual physical activity can increase longevity, and that long-term running lowers the risk of cancer and neurological disease. Data indicate that higher levels of physical activity are more important than body fat as a predictor of all-cause mortality. As the “graying” of the North American population continues, it will become increasing important to evaluate exercise programs and integrate optimal ones into society.

**REFERENCES**


INTRODUCTION

Imagine if you will, Hector and Achilles, two great Greek warriors that meet in combat. For the purposes of this discussion, Hector and Achilles are not just highly trained warriors who have spent years honing their skills. Hector, in fact, has the advantage of a resting hematocrit of 49 from episodic blood doping and use of recombinant erythropoietin. His muscle mass has been augmented with the administration of nandrolone and androstenedione. However, one should not feel sorry for Achilles as he has also reaped the benefits of pharmacology. He has utilized amphetamines and carbohydrates sparing insulin growth factors. As the battle begins, Achilles charges in to meet Hector with an amphetamine-fueled fury and tremendous endurance. Although Achilles is the victor, he does not have time to enjoy the fruits of his victory. Instead, he meets an untimely death due to a well-placed arrow shot by a coward named Paris.

In Homer's tale, Paris' hand was guided by the hand of Apollo. But for purposes of this discussion, Paris does not need Apollo's help. His heart is quieted and his hand is steadied with the use of a B1 specific beta blocker that soothes his fluttering heart and stabilizes his tremulous hand. Although this may sound improbable, this is what is now known as the world of modern day athletic competition.

This manuscript will focus on performance-enhancing drugs. These drugs are defined as any pharmacologically active substance that can be used to improve performance, whether it would be in the work or sport venue.

HISTORY

The use of performance-enhancing drugs, or doping agents as they are commonly known, goes back to antiquity. Although doping agents of the 21st century may be more efficient and exotic, in revisiting times of long ago, performance-enhancing drugs were also found. The Incas chewed cacao leaves to sustain their activity. Norse warriors ate mushrooms with muscarinic activity that fueled hallucinogenic-driven rages and morphed men into fearless warriors. During World War II, amphetamines were used by both soldiers and pilots to combat fatigue. It is obvious that the use of performance enhancing drugs has a rather long, albeit, somewhat tempestuous history.

The first controlled studies conducted in 1959 examined the use of amphetamines in distance swimming and cycling. Clear-cut benefits were seen in both events. Just one year later, in the 1960 Olympics, the first documented doping fatality occurred. An athlete experienced an amphetamine-induced stroke during a cycling event.

One of the major issues to address in regards to the field of performance-enhancing drugs is the realization that it has taken some time for the scientific community to catch up with what the athletic community has known for years. Androgenic anabolic steroids are the most common performance enhancing drugs used in strength and sport activities. Notably, anabolic steroids were met early on with skepticism by both physicians and researchers. In a 1972 article published in an issue of the journal Science, Wade noted, “Doctors denounce anabolic steroids but athletes are not listening.” The subsequent publication in 1981 by Ryan carried the title, “Anabolic steroids or fools’ gold.”

Currently, in the 21st century, the research consensus is that performance-enhancing drugs may have a positive effect on strength when combined with muscular training. This continues to show the reticence on behalf of the research community in terms of accepting the capabilities of anabolic androgenic steroids. While an
academic controversy clearly persists, well-developed studies have shown that the systematic use of supratherapeutic doses of anabolic steroids have confirmed ergogenic and anabolic effects. This was clearly demonstrated by the well-controlled and elegantly followed work performed in East Germany between 1966 and 1990. Particular attention was given to the female athletic population and more specifically, the population of Olympic athletes.

Generally speaking, performance-enhancing drugs can be divided into several categories. Stimulants include common substances such as caffeine and over-the-counter agents (i.e., pseudoephedrine and pharmacologic agents that are heavily regulated). Amphetamines and cocaine derivatives are also part of this category. Are you one of the many people who enjoyed a cup of coffee this morning? If you did and you happened also to be an Olympic or international athlete being tested for performance-enhancing drugs at this very moment, you would fail your test, be stripped of your medals, and be sent home in shame. Coffee is a performance-enhancing drug. Other categories of these drugs include agents that build muscle and bone such as anabolic steroids, insulin growth factors, and human growth hormones. Further discussion is warranted in regards to these agents, not only as a group of drugs that are frequently abused, but also as a class of drugs. Additionally, they have the potential to provide significant benefits for treatment of certain diseases and conditions.

With any performance-enhancing drug, masking agents are typically involved. The most common masking agents include diuretics and epitestosterone. Diuretics are not only useful for weight reduction, but can also be used as a masking agent. They offer the benefit of increasing the clearance rate of water soluble steroids, making it potentially more difficult for a steroid to be detected. The final group of performance-enhancing drugs consists of agents that increase oxygen delivery. This category includes erythropoietin, blood doping, and/or artificial oxygen carriers.

A brief history of performance-enhancing drug use and abuse reveals a rather checkered history, particularly in the field of cycling. In the 1800s, it was not uncommon for cyclists to use a combination of cocaine and heroin for long distance events as a way to control pain and maintain their vigil. There was, however, a risk for overdose, and in 1886, Arthur Linton died during a competition for this very reason. In 1924, the Pelissiers demonstrated to a visiting journalist their cocaine, heroin, and chloroform cocktail, something commonly used during racing events.

This information solidifies the notion that performance-enhancing drugs have been around for quite some time. The question then becomes when it was that anabolic androgenic steroids first came in to use. A literature review reveals that as far back as the late 1800s, Brown Sequard injected aqueous extracts from animal testes and claimed to have reversed his own aging process. This may have been more placebo than reality, but it did indicate that even at that time there was a desire to enhance performance. In World War II, German soldiers were not only routinely given amphetamines, but also testosterone to increase stamina and aggression.

In 1939, Butenandt and Ruzicka were awarded the Nobel Prize in chemistry for the synthesis of testosterone. In 1956, John Ziegler, an American physician, returned from a weightlifting competition with knowledge about the use of anabolic steroids that had been passed on by a Russian physician. Subsequently, he returned to the United States and began work with CIBA pharmaceuticals to develop the first anabolic steroid to be used and abused as a synthetic steroid. He is the grandfather of the synthetic steroid that is generically known as methandrostenolone. By the mid 1960s, other companies raced to develop similar agents.

In this day and age, there is not only anabolic steroid use by athletes, but also by nonathletes. A household survey conducted in 1991, and repeated in the late 1990s, and again in the early 2000s, showed a steady increase of anabolic steroid use by nonathletes. In 1991, it was noted that approximately 1 million people used anabolic steroids. The most recent estimates in the 2000s revealed that approximately 3 to 3.5 million people use anabolic steroids in the United States. Depending upon the particular data referenced, use amongst young Americans taken across a broad spectrum notes that almost 3% of the youth population have taken an anabolic anabolic steroid at least once. That number rises to between 15% and 30% in the community of weight trainers. Particularly staggering is the fact that 10% of these users are teenagers. Even though all of the medications utilized are schedule III drugs that have been tightly regulated since 1990, they remain readily available and are widely used.

ANDROGENIC ANABOLIC STEROIDS

Androgenic anabolic steroids are all basically derivatives of the parent compound, testosterone. Making mere structural changes and rearranging component parts allows one to make subtle adjustments to testosterone and augment its utility. In all instances, modifications to testosterone are performed with several goals in mind. The first goal is to alter the anabolic androgenic potential and augment the anabolic potential. The second is to slow the inactivation of the drug. The third goal is to decrease the rate of aromatization to estradiol in order to negate the androgenic and anabolic effects.

Generally, steroids are administered as either an intramuscular or an oral preparation. All oral agents are typically 17-alpha alkyl derivatives, and include methandrostenolone, methyltestosterone, oxandrolone, oxymetholone, and stanozolol. Injectable agents are usually 17-beta estradiol derivatives and include nandrolone decanoate, methenolone, stanozolol, and boldenone. The physiology of anabolic androgenic steroids also needs to be addressed. In normal males, the typical production of testosterone ranges anywhere from 4 to 10 mg per day. Females produce testosterone in a range from 0.4 to 0.12 mg per day. Testosterone is a normal hormone and has normal function that is critical to various stages of life. In the embryonic stage, it is involved in sex determination and is primarily androgenic at that point. During puberty, testosterone is responsible for the development of secondary sexual characteristics and has an androgenic effect. It also regulates many
Additional physiologic parameters that are impacted by anabolic androgenic steroids include the effect they have on the androgen receptor. It was previously thought that at physiologic doses, testosterone saturated the androgen receptor. It is now known that exposure to androgen increases the androgen receptor number. The net outcome appears to be a positive feedback loop. More specifically, when one looks at anabolic androgenic steroids and strength training, there appears to be a clear interrelationship between the androgen receptor and strength training. Bamann and colleagues published a rather elegant study in the American Journal of Physiology in 2001. Researchers looked at the androgen receptor before and after concentric and eccentric loading of vastus lateralis muscle. Percutaneous muscle biopsy was performed 48 hours post exercise. It was noted in all instances that with strength training, there was an increase in the number of androgen receptors from the vastus lateralis muscle. This was further noted to be augmented with the use of anabolic steroids. Work performed by Bhasin and colleagues noted that in a group of 43 men randomized to 4 groups, the combination of exercise and supratherapeutic doses of testosterone resulted in rather dramatic changes in muscle mass, leg press strength, and cross-sectional area of measured muscles. Of particular note was that improvements were seen even in the group that did not exercise. The most robust improvements were seen in the group that combined supratherapeutic doses of steroids and exercise. However, even in the group that had only supratherapeutic doses of steroids, rather robust changes were noted. This clearly indicates that anabolic androgenic steroids in and of themselves have the ability to positively impact muscle building and strength gains. This was demonstrated at all dosing levels of steroids and followed a dose-dependent curve. The higher doses of steroids yielded more significant changes in quadriceps mass, leg-press strength, and thigh muscle volume. At this point, it is unknown which mechanism allows an increase in muscle mass and volume that can occur both with and without exercise. In a 2001 study reported in the American Journal of Physiology, Endocrinology, and Metabolism, biopsies were performed in a double-blind, placebo-controlled randomized group of 54 men who were injected weekly with testosterone. A biopsy of the vastus lateralis muscle was performed, and in all instances it was noted that there were significant differences in cross sections of both type 1 and type 2 fibers. This relationship followed a direct dose-dependent relationship for the steroids. A direct relationship and an increase in the number of myonuclei in the muscle fibers was also noted.

Another fascinating anabolic steroid study was completed in 1999 and published in the American Journal of Sports Medicine. It specifically attempted to determine the effect of anabolic steroids on healing muscle contusion injuries. The work, conducted by Beiner, compared three groups with muscle contusion injuries. Groups were given either a one-time dose of a placebo, nandrolone, or methylprednisolone. In all instances, the group that was given the nandrolone was noted to have a rather significant positive effect on the amount of force and torque that could be generated in the muscle that had sustained the contusion injury. Of particular note was that in all instances, the corticosteroid group showed a significant negative effect. Clearly, there is a specificity issue in this instance where an anabolic androgenic steroid had a significant positive effect and a glucocorticoid had a negative effect.

Looking at a summary of the effects of anabolic androgenic steroids on the muscular system and tendonous system, there is a tendency to note that anabolic androgenic steroids have a potentially negative impact on tendons. Testosterone has been shown to increase synthesis and production of type 1 collagen, promote upper regulation of type 3 collagen as well as the upper regulation of collagen crosslinks. This occurs in concert with increasing muscle mass, muscle volume, and muscle strength in a dose-dependent manner. This has been shown in a rather robust fashion in multiple journal articles over many years. As noted in several case reports, there appears to be an increased risk for tendon rupture in individuals who have taken steroids in supratherapeutic doses. However, this is considered a rather rare injury and the exact mechanism by which it happens remains open for discussion. It is believed that anabolic androgenic steroids have an effect on tendons and potentially increase the risk for rupture by virtue of the fact that they may cause a decrease in matrix metalloproteinases that affect tendon remodeling. In essence, a scenario is created where the ability of the tendon to remodel and respond to cyclical eccentric loading in the phase of increasing muscle mass and muscle strength is lost. Clearly, that would seem to lead towards the potential for tendon rupture. Animal studies suggest that collagen dysplasia results from exposure to androgenic anabolic steroids and results in a thicker and less compliant tendon. This has been noted in supraphysiologic dosing of anabolic steroids and animal studies, but to date, the human literature is quite sparse.

Physicians must understand that despite the best admonitions, athletes and nonathletes will continue to use performance enhancing drugs. Work published in Sports Illustrated in 1997 asked two simple questions. The first question was: “What if you could take a performance enhancing drug, not get caught, and it would allow you to participate and win an Olympic medal, would you take it?” Of the Olympic athletes polled, 98% answered yes. The second question was: “If you could achieve all of the things that were noted in the first question, but the use of this medication or drug would dramatically and negatively impact your life expectancy, and if you knew you would not get caught, would you continue to take the drug?” Of those polled, 75% answered yes. If that is the case, physicians have a responsibility to inform athlete and nonathlete populations alike about steroid use. It is not uncommon for athletes to take anabolic steroids in supraphysiologic doses or to take them in two ways in an attempt to avoid side effects.
for “drug on” and “drug off” times (also known as drug holidays), to minimize adverse side effects. The route of administration for cycling is interesting to note. The vast majority of anabolic steroid users (75% and 90%), self administer intramuscular (IM) formulations. It was found that 90% of anabolic steroid users stack anabolics and use them in concert with other performance-enhancing drugs such as growth hormones, insulin, amphetamines, and thyroid supplements. The data on growth hormone, insulin, and insulin growth factor is not nearly as well established as for anabolic androgenic steroids.

One of the major dilemmas in the field of performance-enhancing drugs is understanding why athletes take these substances. Part of the answer is a lack of conclusive studies that demonstrate the risks and benefits of these drugs. Initial denial of the efficacy and benefits of anabolic steroids when they first came into use in the 1960s may be at the root of the problem. Another factor contributing to their use is that by designating them schedule III drugs, a black market has been created.

Androgens were specifically banned by the International Olympic Committee in 1974. Initial testing on athletes for steroid use was performed using gas chromatography and mass spectrometry urine analysis. It was a rather difficult mode for testing because exogenous and endogenous testosterones were indistinguishable. As a result, a new test was developed in 1984 that enabled testosterone and epitestosterone levels to be compared as a ratio. By 1984, gas chromatography, mass spectrometry, and the ratio of testosterone and epitestosterone were used for Olympic athlete screening, all of which would become standard practice over time.

Looking in more detail at a program that is extremely well developed, highly organized, structured, and has emphasis on the use of androgenic anabolic steroids in athletes, like the East German program referenced earlier, the results become rather staggering. More specifically, the results in women become rather remarkable. In a well developed program with the administration of supraphysiologic doses of anabolic steroids, dramatic performances were seen in all arenas. In track events, staggering changes were noted. In 100 m sprinting events, times had improved by as much as 7/10th of a second. In the 400 m, 800 m, and 1500 m running events, improvements in time of 4 to 5 s, 5 to 10 s, 7 to 10 s were noted, respectively. The improvements were observed in both men and women, with the greatest changes seen in women. Staggering results were also noted in weight events and throwing events. Gains of 2.5 to 5 m were noted in the shot put, 6 to 10 m in the hammer throw, 8 to 15 m in the javelin throw, and a staggering 10 to 20 m in the discus throw. Once again, the most dramatic changes occurred in the female population. The impact was immense. During the Olympic Games of 1972, 1976, 1980, and 1988, East Germany garnered 144 gold medals, 120 silver medals, and 120 bronze medals over that time span. The most dramatic changes were observed in the swimming pool. In the previously specified Olympic years, the women of East Germany won 32 out of 43 gold medals. This program was not without its side effects, however. Reports of abnormal births, psychiatric disorders, pre-
63 women after open reduction, internal fixation of subcapital hip fractures, or intertrochanteric hip fractures. Thirty-five women in the group had subcapital fractures and 28 had intertrochanteric hip fractures. They were randomized to a 1-year treatment with nandrolone (25 mg every 3 weeks), vitamin D, and calcium or calcium only. Outcome measures all conclusively showed that the anabolic steroid group had significant improvement at 6 and 12 months of thigh muscle volume and a quantitative computed tomography scan for bone mineral density which calculates with dual energy X-ray beam absorptiometry. Interestingly enough, a decrease in the rate of falls was also reported.

Clearly, when examining anabolic androgenic steroid use, it isn't a simple question of it being good or bad. As with any medication used appropriately, there may potentially be extended beneficial effects. However, if misused or abused, a raft of unacceptable side effects may be created. These side effects make it difficult to endorse these medications with the restrictive guidelines and control parameters that are currently in place.

**BLOOD BOOSTING**

Blood boosting can be accomplished through the utilization of blood doping or through such substances as erythropoietin or erythropoietic agents. The group of athletes that would typically benefit from blood boosting are endurance athletes. These athletic events involve significant aerobic energy production. In all instances, performance would be limited by the potential for oxygen delivery and utilization by active muscles. In well-trained athletes, the limiting factors on oxygen uptake are the cardiac output and oxygen carrying capacity of the blood. Studies performed in the 1960s clearly demonstrated the physiology of the athlete as well as the physiology of the nonathlete. The VO2 max is the maximal oxygen (O2) uptake an individual is capable of obtaining. This is measured in liters per minute. The equation expresses the rather important fundamental relationship between an oxygen uptake at the tissue level, VO2, and cardiac output. The formula described is the Fick equation: VO2 max is equal to cardiac output (CO) x O2 content of the arterial side of the circuit minus O2 content at the venous side of the circuit [VO2 max = CO x (O2a-O2v)]. Saltin and colleagues in The Journal of Applied Physiology going as far back as 1967 demonstrated very high VO2 max values in elite athletes. This work was subsequently collaborated by Ekblom in the same journal in 1968. He not only demonstrated very high VO2 max values in elite athletes, but also demonstrated very high CO measures in elite Swedish aerobic athletes.

Ekblom and colleagues raised a very interesting question regarding what would happen when one has blood loss and then reinfusion at a later date. In a rather elegant study published in the 1972 issue of Journal of Applied Physiology, 1972, maximal work performance was measured after blood loss and performance after reinfusion 4 weeks after blood loss. Not surprisingly, there was a rather predictable decrease in performance capacity following blood loss. After reinfusion, there was “overnight increase” in VO2 max and performance capacity.

After realizing the potential ramifications in regards to athletic performance, the concept of blood boosting was born.

Speculation has run rampant in this field going as far back as the early 1970s. Though it was never proven, it was alleged that the great Finnish runner, Lasse Virén, who was the winner of both 5000 and 10,000 meter run in the Munich and Montreal Olympics was blood boosting. In 1984, the United States Men’s Olympic Cycling Team garnered a record of nine medals in the depleted field that led to admission of widespread blood boosting.

As a result, blood boosting or blood doping was banned from international competitions in 1986. With that, some rather entertaining and interesting events unfolded over the years. In the 2002 Winter Olympics, the entire Austrian men’s cross country team was found with transfusion equipment. They claimed to be using the equipment for ultraviolet radiation treatment and disease prevention. Needless to say, the coach, team physician, and the entire team were sent home. The coach and team physician were permanently banned from the Olympics.

Blood doping has risks and benefits. It should be noted that blood viscosity increases exponentially with the increased hematocrit above 40. Stone and colleagues in the American Journal of Physiology in 1968 showed quite conclusively that viscosity increases vascular resistance, independent of vessel diameter. Significant to these findings is that increasing blood viscosity clearly leads to an increased risk for thrombosis, myocardial infarction, deep venous thrombosis, and pulmonary embolism. In fact, individuals who have polycythemia vera have hematocrits routinely greater than 55. Routine phlebotomy is performed aggressively in hopes to control hematocrit levels and prevent the sequelae.

**ERYTHROPOIETIN**

Erythropoietin (EPO) is a glycoprotein hormone that is produced mainly by the cells of the peritubular capillary and the lining of the kidneys. It is stimulated to production by a reduction in renal artery circulation and is responsible for regulation of red blood cell production and marrow stimulation. The gene for this hormone was cloned in 1985, leading to the development of recombinant hormone or recombinant EPO. In today’s medical arena, EPO is used to treat anemia associated with chronic renal failure, anemia status post chemotherapy, or anemia associated with systemic diseases such as HIV. With EPO, chronic anemia patients require fewer transfusions and have increased exercise tolerance.

The question at this point is what advantages EPO would hold for an athlete as opposed to blood doping or reinfusion of a patient’s old blood. There are technical advantages to the athlete. First, there is no need for withdrawal of one’s own blood to practice reinfusion. With that, there is no reduction in performance that would accompany the blood donation. Detectability is limited in that EPO is a naturally occurring peptide, has very favorable pharmacokinetics, and has a very short half life which makes it difficult to detect. Safety and efficacy of recombinant EPO and EPO in general has.
been demonstrated with regular EPO dosing in healthy subjects. Bergland and Ekblom in the Scandinavian Journal of Medicine Science and Sports in 1991 looked at the effect of EPO administration on maximal aerobic power and healthy subjects. They found that EPO improves run time to exhaustion on recreational treadmill test by 17%. The same findings would be anticipated exclusively in athletes.

It has been clearly demonstrated that there is an increase risk for thrombosis, stroke, and nonfatal myocardial infarction. This may be due to the fact that EPO taken in supraphysiologic doses raises hematocrit to dangerously high levels. Between 1987 and 1991, there had been a total of 18 deaths in competitive cycling. Twelve of these have occurred with Dutch cyclists, and interestingly, EPO use was rampant during that time, particularly amongst the Dutch cyclists.

GENE TRANSFER TECHNOLOGY

As we edge further into the 21st century, the arena of gene transfer technology needs to be examined. Gene transfer technology, or at least the concept of it, dates back as far as 1964. In 1964 in the Winter Olympics, a Finn by the name of Eero Mantyranta won 2 gold medals in cross country skiing. He had an advantage over everyone. Testing that was performed 30 years later revealed that he and many of his relatives had a genetic mutation for the gene encoding for the EPO receptor. The normal feedback control for EPO was disrupted. He and his family had resting hematocrit values significantly elevated 20% above normal levels. So the question becomes, how would the mutation be created if someone is not born with it? In 1997 Svensson and colleagues demonstrated long term expression of EPO in rodents and nonhuman primates following intramuscular injection of a replication defected adenoviral vector. Svensson and colleagues used an adenovirus vector to deliver EPO genes to mice and nonhuman primates. Hematocrits elevated 49 to 81% in mice and 40 to 70% in primates. This effect persisted for 1 year in the mice and 12 weeks in primates without any noted deleterious side effects.

So what is the appeal of gene transfer technology to athletes? As can be seen from the mice and the nonprimate model, less frequent dosing leads to less likely detection. This is potentially technically simple to perform as it becomes more readily available. It would be difficult to screen for, as it would also require a muscle biopsy to demonstrate the presence of the virus. Given the fact that the result and effects are further “downstream,” changes in EPO to red blood cell mass could be attributed to other means; namely “I knew I was going to be hard pressed to win this sporting event so I went to the Rockies and I trained at 10,000 feet.”

CONCLUSION

In conclusion, when looking at performance enhancing drugs, it is important to realize this is a rather large and somewhat overwhelming field. It may include over-the-counter medications, vitamins, minerals, and supplements that may be highly speculative. Vitamins and minerals have become standard and routine agents that many people take every single day. Speculative agents include such things as creatine, but to date, there has been no data to establish its efficacy. Caffeine is one of the oldest stimulants known to mankind. It is banned in the Olympics, yet it also has a very well developed track record for efficacy and safety.

This what is known about anabolic steroids and erythropoietin agents.

1. Anabolic steroids appear to be effective in increasing muscle size, muscle mass, strength, as well as increasing bone mass.

2. Side effects of anabolic steroid use have yet to be conclusively demonstrated.

3. Anabolic steroids are widely abused and continue to worsen at the professional college and high school level, despite ongoing efforts to educate about abuse.

4. Anabolic steroids may have great potential in treating acquired immune deficiency syndrome-related sarcopenia, recovery after injury or surgery, and in combating osteoporotic fracture. Blood doping and EPO use and the use of novel concepts that increase blood volume have clearly had an impact on aerobic performance.

BIBLIOGRAPHY

INTRODUCTION

The hallmark of most neuromuscular disorders is progressive muscle atrophy and weakness leading to substantial impairment and disability. Many of these disorders are slowly progressive, with weakness developing over the course of many years (e.g., Charcot-Marie-Tooth [CMT] disease, limb-girdle muscular dystrophy [LGMD]). Others progress more rapidly (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]).

Recent years have seen great strides in understanding the biological processes underlying various neuromuscular diseases, but few curative treatments exist, and the handful of available pharmacological options (e.g., riluzole for ALS, corticosteroids for Duchenne muscular dystrophy [DMD]) have a minimal effect on the course of disease progression. With rehabilitation interventions the main treatment for individuals with these disorders, exercise, particularly resistance training to increase or maintain muscle mass and strength, is of great interest as a way to retain the highest levels of ability and function.

At the same time, ongoing concern surrounds the potentially harmful effects of moderate to high-intensity exercise for patients with neuromuscular disorders, and evidence on specific exercise prescriptions for different patient populations is scarce. This author commonly reviews patients with various neuromuscular disorders who have been instructed by physicians, therapists, and web-based resources to do no exercise beyond activities of daily living (ADLs).

Regardless of the underlying cause or pace of disease progression, muscle weakness is a cardinal feature of most neuromuscular disorders. It eventually leads to disability that affects day-to-day activities, occupational tasks, and recreational pursuits. Exercise therapy might reverse or ameliorate the damage.

This manuscript examines the potential role of exercise in disorders affecting skeletal muscle, the motor neuron, and motor axon. It discusses the effects of resistance training on improvements in strength, endurance, and ADLs, and briefly covers aerobic exercise. It reviews evidence for and against exercise therapy, and provides recommendations for the practicing clinician.

OVERUSE WEAKNESS

Overuse or overwork weakness, first identified in patients recovering from the effects of poliomyelitis, is a major concern among patients, their families, clinicians, and therapists. Anecdotal case reports suggest increased weakness following strengthening exercise in ALS, peripheral nerve lesions, and DMD.19,20,29
One such report on several family members with fascioscapulohumeral dystrophy (FSHD) indicated overuse based on asymmetric weakness in the upper extremities. Those affected showed greater weakness on the dominant side, with the exception of a heavy equipment operator who used his nondominant left arm to operate equipment and had more weakness on that side. This case, however, fails to take into account the common finding of significant asymmetry in the pattern of weakness typically found in patients with FSHD.

In one study, patients with DMD performed submaximal knee extension exercise for 6 months and showed no evidence of overuse weakness compared to nonexercised controls. No definitive evidence exists at this time to support overuse weakness in patients who have myopathic disorders with mild to moderate weakness. It is prudent, however, to adapt exercise programs to their individual needs and have adequate supervision and monitoring.

**RESISTANCE EXERCISE IN RAPIDLY PROGRESSIVE MYOPATHIES**

DMD is marked by rapid and progressive loss of strength and functional capacity. Boys are typically dependent on wheelchairs for mobility between the ages of 8 and 12 years. Because of the rapid progression, they are limited in their ability to participate with their peers in normal age-appropriate physical activity and play. This poses considerable risk of isolation and lack of social interaction, as well as the additive problems of disuse weakness and atrophy. Obesity from inactivity, potentially complicated by corticosteroid use, puts patients at further risk. Thus, there has been considerable interest in the potential benefits of strengthening exercise to slow the progression of weakness, improve functional capacity, and potentially allow for fuller participation in society.

In general, data show that resistance exercise in children with DMD either maintains strength or results in mild improvement. However, there is little consensus among experts on the clinical utility of strength training in this population. The few studies in the literature are limited by: (1) frequent use of nonquantitative, insensitive outcome measures; (2) often poorly defined exercise programs; (3) lack of a control group in many cases, or use of the opposite limb as a control; (4) heterogeneity in the treatment groups regarding age, disease progression, functional level, and degree of contracture; and (5) small sample sizes in treatment and control groups. Additionally, any intervention trial directed toward DMD must take into account the rapidly progressive nature of the disease.

Pioneering studies by Abramson and Rogoff and Hoberman examined resistance exercise in children with DMD. In both reports, strength was assessed by manual muscle testing. In response to a 7-month program of active, active-assisted, and resistance exercise performed 3 times per week, 50% of the subjects improved slightly by about one-half to one grade on the Medical Research Council (MRC) scale; the other 50% remained unchanged. Although this study was uncontrolled and poorly quantified, it showed improved mobility in 8 of 27 subjects. In an uncontrolled study, Hoberman examined 10 patients over 4 months in a daily program of resistance exercise, gait training, and stretching. Strength improvement was defined as one full MRC grade. Data showed no reported gains in strength, but some patients declined less during the intervention than in the previous year.

The lack of positive results in this study and the 50% nonresponse rate in the Abramson and Rogoff trial may have been influenced by the high proportion of subjects with severe disease progression. Two-thirds of the patients in both studies were confined to wheelchairs. (Data show that by the time patients with DMD are wheelchair dependent, they have lost half of their muscle mass.) Contractures in the majority of patients further reduced the ability of the muscle to optimally respond to resistance exercise training.

Vignos and Watkins examined the effects of a 1-year, home-based, higher-intensity resistance-training program in still-ambulatory patients with muscular dystrophy (14 DMD, 6 LGMD, 4 FSHD). The DMD patients were compared to a nonexercised control group of DMD patients of similar age, strength, and functional ability. Manual muscle testing showed measurable increases in strength in all patient groups.

Gains in the three muscular dystrophy groups occurred in the first 4 months, and were maintained during the subsequent 8 months. In general, patients with less severe disease improved the most, with greater progress in muscles that were initially stronger. In the year prior to the program, muscle strength had declined in both groups. Control subjects continued to experience decline during the second year, while the exercise group showed no loss in strength and a minimal increase. These outcomes suggest long-term benefit.

Delateur and Giacconi isokinetically trained the quadriceps in one leg of four patients with DMD 4 to 5 times per week for 6 months. The nonexercised leg served as the control. All four subjects were ambulatory at the onset of the study and had at least grade 3/5 strength in the knee extensors. However, one subject with rapidly progressive disease became nonambulatory during the study. Strength was tested on the same device at monthly intervals during the 6-month training period and for the first 6 months post-training, and at 18 and 24 months post-training.

The subject who deteriorated rapidly during the course of the study likely biased this small data set. However, findings showed modest increases in maximal strength. This gain was statistically greater in the exercised leg at only the 5- and 9-month test periods, but the maximal strength of the exercised legs was equal to or stronger than that of the control legs for all months of follow-up except 2
years. In addition, there was no evidence of overuse weakness in the trained legs compared to the control group.

In summary, little evidence supports overuse weakness in response to controlled resistance training programs, at least in DMD. For the most part, studies have shown either maintenance of strength, or in some cases, modest improvements. The most significant gains have been in patients with less disease progression and in the less severely affected muscle groups. These outcomes suggest the need to intervene as early as possible to obtain maximal benefits.

Outcomes to date warrant further investigation into the potential benefits of resistance exercise in DMD. Such studies will need adequate sample sizes, matched controls, carefully designed and monitored programs, and sensitive strength and functional outcome measures. They will also need to take into account the fact that most boys with DMD are now treated with either oral prednisone or deflazacort. The additive effect of well-controlled resistance training programs in conjunction with corticosteroids has not yet been assessed. However, daily stretching to limit the progression of joint contracture is recommended by most experts.

**RESISTANCE EXERCISE IN SLOWLY PROGRESSIVE MYOPATHY**

In more slowly progressive myopathies, such as myotonic dystrophy (DM1), LGMD, FSHD, and most of the congenital myopathies, the goal of resistance exercise programs has been to improve strength and function rather than simply slow the pace of disease progression. The majority of these studies have grouped patients with different disorders to achieve adequate sample sizes.

McCartney and colleagues36 dynamically trained the elbow flexors with different disorders to achieve adequate sample sizes. The majority of these studies have grouped patients with neuromuscular diseases as a number of the isokinetic indices for the elbow flexors failed to show any statistical improvement. It should be noted, however, that there was no improvement in the majority of isokinetic elbow flexion variables in the healthy controls either. This could be related to the lack of similarity between the training and testing regimens (isotonic vs. isokinetic). Therefore, the concern over higher-intensity training may not be valid.

Subjects with DM1 showed no deleterious effects from training, and all progressed with regard to their training loads. None of the less-specific outcomes (maximal voluntary isometric contraction [MVIC], isokinetic strength, or timed functional tasks) exhibited any significant improvement. Myoglobin levels were not significantly changed from pretraining levels.

A study by van der Kooi and colleagues51 randomized 65 patients to one of four groups: training and placebo; training and albuterol; nontraining and placebo; and nontraining and albuterol. The authors hypothesized that the strength-increasing effect of albuterol, a [beta]2-adrenergic agonist, might be augmented when combined with resistance exercise. Participants completed a home-based, individualized program of dynamic and isometric resistance exercise for the elbow flexors and dorsiflexors. All subjects had > 3/5 MRC strength for the elbow flexors and > 0/5 for dorsiflexors. There was a significant improvement in elbow flexion of 1RM in the training group but no change in the primary outcome measure of elbow flexion MVIC. Dorsiflexion strength declined for both measures. There was no evidence of improvement in functional tasks or any significant harmful effects from training.

Aitkens and colleagues3 investigated a moderate-resistance, home-based exercise program for patients with slowly progressive neuromuscular disease. Subjects trained their knee extensors and elbow flexors unilaterally with weights 3 days per week for 12 weeks. A healthy control group was studied for comparison. Training loads of moderate intensity ranged from 10-40% of maximum (except handgrip at 100%). Both treatment and control groups demonstrated modest increases in strength, with similar gains for both the exercised and nonexercised limbs.

Lindeman and colleagues32 examined the effects of a 24-week strength training program in patients with DM1 and hereditary motor sensory neuropathy. Matched subjects were randomly assigned to either a training or control group. The former performed knee extension exercise 3 times per week with loads increasing gradually from 60-80% of maximum. Maximal isometric and isokinetic strength, functional tasks, ADL questionnaires, and serum myoglobin were measured pre- and post-training.

Subjects with DM1 showed no deleterious effects from training, and all progressed with regard to their training loads. None of the less-specific outcomes (maximal voluntary isometric contraction [MVIC], isokinetic strength, or timed functional tasks) exhibited any significant improvement. Myoglobin levels were not significantly changed from pretrained levels.
Exercise Therapy in Neuromuscular Disease – Why Bother?

CHARCOT-MARIE-TOOTH DISEASE

CMT, or the hereditary motor sensory neuropathies (HMSN), encompass a family of inherited peripheral neuropathies that present with slowly progressive distal to proximal muscle atrophy and weakness. CMT disease type 1A (CMT1A) is characterized by markedly slowed conduction velocities in motor and sensory nerves (often 15-20 m/s), areflexia, and progressive motor and sensory deficits by the mid-teens in most cases. CMT disease type X (CMT-X) presents with similar clinical features, but intermediate nerve conduction slowing.

Alternatively, CMT disease type 2 (CMT2) encompasses a number of disorders where the primary pathology is within the axon rather than the myelin (e.g., mutation in Mitofusin 2 for CMT 2A). But whether the primary pathology is within the myelin or axon, the eventual disability is secondary to progressive axonal loss resulting in motor and sensory deficits. This may be compounded by other causes of weakness, including disuse atrophy and deconditioning. To date, there are no effective pharmacologic therapies for any of the inherited neuropathies, so rehabilitation interventions, including resistance exercise, are the mainstays of treatment.

A number of studies have investigated resistance exercise in patients with CMT. In general, these have had a number of shortcomings. Lindeman and colleagues carried out the most methodologically sound and comprehensive study. It also included a group with DM1, but the groups were analyzed separately. Subjects matched on baseline strength were randomized to a training or control group. The former performed knee extension, flexion, and hip abduction exercises with weights strapped to the limb 3 times per week for 24 weeks. Outcomes included isokinetic knee extension and flexion torque as well as functional performance, e.g., timed tasks.

Whereas the DM group showed no improvement in torque or function, the CMT group demonstrated gains in torque but not function. There was no evidence of muscle damage as measured by serum myoglobin levels. During the first 8 weeks of training, the maximum surface electromyography (EMG) signal increased substantially, suggesting that the increased strength 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 subjects were randomized to resistance training and placebo or training and 5 gm per day of creatine supplementation. There were no differences between the groups for any outcome. For the groups combined, exercise training increased type 1 muscle fiber diameter, strength, and ADL times. Thus, patients responded to resistance training with muscle fiber adaptations, and improvements in strength and function. Creatine was not beneficial. In a randomized double-blind trial, these same authors demonstrated the benefits of a home-based, resistance training program on ADL function for patients with CMT. They also provided a template for training intensity based on ADL performance (chair rise-time).

Overall, reasonable evidence suggests that progressive resistance exercise can improve strength (at least in larger proximal muscles) and possibly function in patients with mild to moderately severe CMT. Given the underlying pathophysiologv, it is questionable whether resistance exercise could improve strength and function in the more severely affected distal muscles.

POST-POLIO SYNDROME

Effective vaccination programs have eliminated paralytic poliomyelitis, an infectious disease of the anterior horn cell, in the Western world, and its worldwide incidence has decreased dramatically. However, the past 20 years have seen growing acceptance and recognition of new motor deterioration after long periods (often decades) of relative neurological stability in prior paralytic polio patients. In addition, many patients with the so-called PPS experience neuromuscular fatigue, central fatigue, and pain. Reports indicate that as many as 60% of those affected by prior polio may develop new weakness. A 1987 survey identified more than 600,000 prior polio patients in the United States, making PPS a common disorder of the motor neuron.

A full review of the pathophysiology of PPS is beyond the scope of this manuscript. In brief, there are two leading hypotheses. The first suggests progressive deterioration of the distal motor axons in the greatly enlarged motor units. This is supported by single-fiber EMG (SFEMG) observations as well as data from muscle biopsies. The second hypothesis is that loss of entire motor units leads to new onset weakness. Aging alone is associated with significant motor unit losses; those with prior polio, who have fewer and larger motor units, suffer a substantially greater impact. This "accelerated aging" hypothesis is based largely on electrophysiological data from longitudinal studies. Other contributing factors to weakness include disuse, pain inhibition, overuse of severely affected muscle groups, and immunological mechanisms.

It is not surprising that resistance exercise is often considered when designing rehabilitation programs for those with PPS. New motor deterioration often adds to or worsens disability that affects ADLs, occupational, and recreational activities. Therefore, any intervention that might lead to functional improvement is of great interest.
Early reports on resistance exercise were often single-case studies or uncontrolled trials with small sample sizes. Most of these showed improved strength. However, some noted overuse weakness and cautioned against exercising severely weak muscles. A number of more recent studies have examined PPS strength training in a more controlled fashion. In general, outcomes have been positive. None, however, included any evaluation of the potential negative effects on the motor unit itself.

In a comprehensive study, Agre and colleagues examined the potential benefits of a 12-week, home-based program of quadriceps training in 12 men and women with clinical feature of PPS, all of whom had at least grade 3+ strength on manual muscle testing and features consistent with prior polio on electrodiagnostic assessment. They reported an overall mean increase in weight lifted of 61%, but no significant improvement in the less specific isokinetic or isometric peak torque measures for the knee extensors. Creatine kinase (CK) values did not change, and there was no increased jitter, blocking on SFEMG, or change in the macro EMG amplitudes. No evidence was found to show that the program adversely affected the motor units or the muscles as the EMG and CK did not change.

Chan and colleagues randomized five subjects with clinical and electrodiagnostic features of PPS to 12 weeks of isometric training of the thenar muscles or a nonexercising PPS control group. Subjects underwent comprehensive examination at baseline with motor unit number estimates, maximal voluntary and evoked force measures, and twitch interpolation to assess adequacy of motor unit number estimates, maximal voluntary and evoked force measures, and twitch interpolation to assess adequacy of central drive. Significant improvements in strength in the PPS training group were largely explained by increased central drive. There was no indication of further motor unit loss as a result of the training.

Evidence suggests that strength training is 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 motor neurons. The disease often presents with focal weakness limited to one limb. It eventually spreads to other segments of the limb and becomes generalized. The hallmarks of ALS are muscle atrophy and weakness from lower motor neuron loss, and weakness, fatigue, and spasticity from upper motor neuron involvement. The overall incidence ranges between 0.4 to 2.4 cases per 100,000. This figure will likely increase as our population ages. Therefore, there is considerable interest in exploring other potential therapeutic interventions that may maintain strength or slow disease progression, and ultimately, either improve function or ameliorate the rate of decline.

Traditional thought based on the rapid progression of weakness in ALS, has been that exercise would be harmful; that severely weak muscles, already functioning at levels close to maximal voluntary contraction force when simply performing ADLs, are more susceptible to overuse injury. Therefore, some experts have recommended that patients with ALS do no exercise beyond that required for day-to-day activities. However, recent studies using animal models of motor neuron disease provide evidence that endurance exercise slows disease progression. Kirkinezos and colleagues reported that treadmill running 5 days per week at 13 m/min led to a significant increase in the lifespan of G93A-SOD1 male (but not female) mice. Similarly, Veldink and colleagues found that treadmill running at 16 m/min delayed disease onset and prolonged survival in transgenic low-copy hSOD1 female (but not male) mice. Conversely, high-intensity treadmill running at 22 m/min did not delay disease onset in G93A-SOD1 male or female mice, and shortened lifespan in the males.

Kaspar and colleague demonstrated the most pronounced effects of exercise using the SOD1 mouse model. Mice exposed to an exercise wheel 6 hours per day beginning in the presymptomatic state survived 33% longer than those that weren’t exposed to the exercise. This evidence suggests that low to moderate intensity exercise may be of benefit, but high-intensity endurance exercise may be detrimental.

Very few controlled studies have examined the potential benefit of resistance exercise in patients with ALS. As mentioned earlier, traditional thinking cautioned against therapeutic exercise due to concerns of overuse of denervated or severely weak muscles. However, early case reports with generally positive results have led to at least two controlled studies.

Drory and colleagues investigated a twice daily, home-based, individualized program of modest intensity exercise to improve endurance. It was compared to a usual activities control group. Outcomes showed less deterioration on the ALS functional rating scale (ALSFRS) and Ashworth spasticity scale at 3 months, but no difference at 6 months. At 9 and 12 months, there were too few subjects remaining for analysis.

Bello-Hass and colleagues performed the most rigorous examination of resistance exercise in ALS patients to date. Twenty-seven patients with clinically definite or probable ALS were randomized to a daily stretching and resistance exercise group or a control group that performed daily stretching. Of 27 patients, only 8 resistance exercise and 10 control completed the study. Despite these dropout rates, the resistance training group had significantly higher scores on the ALSFRS and the 36-Item Short Form Survey Instrument (SF-36) physical function subscale, and less decline in leg strength at 6 months. No deleterious effects were reported.

These studies provide some support for resistance exercise as a potential intervention to slow disease progression and maintain higher levels of function in patients with ALS. However, larger clinical trials

...
are required for more definitive evidence and to further examine the optimal exercise modes, intensities, and overall volumes.

**AEROBIC TRAINING IN MUSCLE DISEASE**

While the majority of exercise studies for myopathies have addressed the cardinal features of weakness and muscle wasting with resistance training, a few trials have investigated the potential benefit of aerobic or endurance exercise. Substantial evidence shows that regular moderate intensity aerobic exercise results in reduced risk of cardiovascular disease, obesity, diabetes, and osteoporosis in the able-bodied population. Those with neuromuscular disorders are often at increased risk for these problems due to inactivity, obesity, and in some cases, use of corticosteroids.

Olsen and colleagues reported improved maximal oxygen uptake and training workloads in FSHD patients in a 12-week cycle training program of moderate intensity (heart rate corresponding to 65% of VO2 max). These results are consistent with those for patients with LGMD, DM1, and mitochondrial myopathy.

Johnson and colleagues recently demonstrated a 38% increase in aerobic capacity following a 12-week program of bicycle ergometer training in patients with inclusion body myositis. In some cases, the improvements in endurance carried over to ADLs and quality of life.

These studies suggest that endurance or aerobic exercise training is safe and effective for those with moderately severe myopathies. In general, the relative improvements in aerobic capacity are similar to controls. Whether endurance training is safe and effective for those with severe weakness has not been addressed.

**CONCLUSIONS**

Not all studies have shown consistent positive effects, but in general, moderate-to high-intensity resistance training is associated with improved strength in patients with a variety of myopathic disorders and neuropathic disorders, including some rapidly progressive diseases, such as ALS. Strength gains tend to be greatest for muscles with mild-to-moderate weakness, and are minimal in muscle groups with severe weakness (Table 1).

Strength training programs in populations with neuromuscular disease should be designed by experienced, trained personnel, and be specifically tailored to the needs and limitations of the participants. They should be supervised, at least during the initial stages, and objective monitoring should be in place.

High-intensity resistance training has no advantage over moderate intensity programs, and may lead to a greater likelihood of joint pain, injury, and overtraining. Training the major muscle groups 2 to 3 times per week with intensities of 12 to 15 repetitions at most is appropriate. The required frequency and intensity for maintenance of strength gains has not been adequately addressed. While data suggest that strength gains occur within training programs, evidence on carryover to functional activities is still lacking.

Future high-quality studies are required to better define minimal and optimal training intensities and volumes. These should ideally be randomized controlled trials, with supervised training programs, blinded assessors, and homogeneous training groups. The latter may require a multicentered approach. Functional, patient-centered outcomes are crucial to examine the potential impact of interventions on disability, participation, and quality of life. Training programs and modalities tailored to specific functional tasks have not been addressed in patients with neuromuscular disease, but are worthy of consideration based on results in healthy older adults.

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**Table 1** General resistance exercise prescription guidelines for patients with neuromuscular disorders

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<tr>
<th>WEAKNESS</th>
<th>MRC GRADE</th>
<th>EXERCISE PRESCRIPTION</th>
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<tbody>
<tr>
<td>None to mild</td>
<td>4, 4+, 5</td>
<td>May perform moderate to high intensity resistance exercise with appropriate monitoring</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(12-15 repetition maximum sets)</td>
</tr>
<tr>
<td>Moderate</td>
<td>3, 4 -</td>
<td>May perform moderate intensity exercise with appropriate monitoring (15-20 RM sets)</td>
</tr>
<tr>
<td>Severe</td>
<td>1, 2</td>
<td>Passive and active assisted range-of-motion exercise to maintain range of motion and prevent contractures</td>
</tr>
</tbody>
</table>

MRC = Medical Research Council
REFERENCES


