Exercise for Individuals with Marfan Syndrome

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ABSTRACT

Purpose: Marfan syndrome is an autosomal dominant connective tissue disorder affecting between 1 in 3,000 to 10,000 individuals. Marfan syndrome has widespread effects on the musculoskeletal, ocular, integumentary, cardiovascular, and pulmonary systems because of a defect in the fibrillin proteins of connective tissues. Common problems include joint hypermobility, sclerodactyly, above average height and limb length, lens dislocation, aortic dilatation and dissection, mitral valve prolapse, spontaneous pneumothorax, stretch marks, inguinal hernias, and enlargement of the neural canal in the lumbar and sacral regions. It has been documented that because of connective tissue changes, individuals with Marfan syndrome are at high risk of aortic dilatation and dissection caused by increases in blood pressure and heart rate. Yet, many youth and adults with Marfan syndrome want to participate in physical activity. The hemodynamic changes caused by exercise, especially intense exercise, may increase the tension and stress on the wall of a weakened aneurysm and result in further weakening or rupture of the vessel wall. All of these potential problems may make it difficult for physical therapists to develop safe exercise programs for individuals with Marfan syndrome. Summary of Key Points: This paper provides an overview of the underlying disease mechanisms, medical management of Marfan syndrome, and scientific evidence for the benefits of exercise. In addition, guidelines are provided to assist in prescribing, monitoring, and progressing exercise programs for individuals with Marfan syndrome. A case study is included to demonstrate an exercise prescription for a young adult with Marfan syndrome. Statement of Conclusions: With modifications, exercise can be a beneficial adjunct in the overall medical management of individuals with Marfan syndrome.

Key Words: Marfan syndrome, exercise prescription, case study, physical therapy

INTRODUCTION

Many congenital or acquired diseases can cause changes in the arteries that result in an aneurysm.1 These diseases are usually seen in aging adults but some occur in childhood.1 The most common site for aneurysms is the brain followed by aneurysms of the aorta.1 Many people with aneurysms have no symptoms until a rupture occurs causing massive bleeding.1,2 For those individuals who have symptoms, localized pressure is felt in the head, hypogastric, or low back areas.1,2 The main risks of exercise in individuals with an aneurysm are progressive enlargement of the aneurysm, tearing of the arterial wall, and sudden rupture of the artery.1,4 Individuals who have an aneurysm and the co-morbidity of high blood pressure are at greater risk of arterial rupture.2,1,2 Exercise at low levels appears to show little to no effect on the aneurysm.1 However, high exercise intensities in individuals with known aortic aneurysms, have been shown to create turbulence within the aneurysm and an increase in arterial wall tension.1,5 A high profile Olympic volleyball player with Marfan syndrome, Flo Hyman, died in 1986 while playing volleyball.3 This death led to a renewed caution when managing an exercise program for individuals with aneurysmal disease.

Marfan syndrome is an autosomal dominant connective tissue disorder, affecting between 1 in 3,000 to 10,000 individuals.2,5-9 However, about 15% of cases appear to be caused by new mutations.10,11 These mutations increase in frequency with increasing paternal age. There is variable expression of the clinical manifestations of the disease.7,10 Individuals with Marfan syndrome have a defect in the fibrillin proteins of connective tissue.6,10-12 Because fibrillin is a major component of all connective tissues, the disease affects the musculoskeletal, pulmonary, cardiovascular, ocular, and integumentary systems.5,9,11-15 Musculoskeletal abnormalities include average height above the 97th percentile, scoliosis, kyphosis, pectus excavatum, pectus carinatum, sclerodactyly, and long, thin limbs.5,8,11,14 Joints are hypermobile and subluxations are common.5,8,11,14 Forty percent of cases have enlargement of the neural canal in the lower lumbar and sacral regions.5,11,14 Moderate to severe thoracic cage deformities can cause restriction of ventilation.14,15 Spontaneous pneumothorax is a complication of Marfan syndrome, so avoiding rapid changes in atmospheric pressure is important.5,11,14,15 Individuals with Marfan syndrome have increased risk of aortic dilatation and dissection resulting in death.5,8,11,14 As the aortic diameter increases, so does the risk of dissection.10,11 Other cardiovascular abnormalities are mitral valve prolapse and

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regurgitation, and aortic regurgitation. Cardiac electrical disturbances are commonly found in patients with Marfan syndrome, either as a primary electrical disturbance or as a secondary disturbance due to valvular regurgitation. Lens dislocation is a common ocular manifestation and other ocular features include myopia and retinal detachment. Common integumentary manifestations include stretch marks and inguinal hernias.

Cardiac abnormalities occur in about 60% of adults with Marfan syndrome. The lesions are progressive in nature. The most severe lesions occur in the ascending aorta, the aortic ring and the sinuses of Valsalva. Chronic aortic regurgitation caused by stretching of the aortic valve leads to aortic dilatation and may ultimately cause aortic dissection and death. The greater the aortic diameter, the greater the risk of aortic regurgitation. Regurgitation rarely occurs with an aortic diameter less than 40 mm. Weakening of the aortic wall is related to a loss of elastic fibers in the media layer. The rate of dilatation is unpredictable. Children have a much lower incidence of being affected by aortic root abnormalities than adults. Mitral valve prolapse can lead to mitral regurgitation, which may be more common than aortic regurgitation, especially in children. Women with Marfan syndrome have a higher incidence of mitral valve prolapse than men with Marfan syndrome. Isolated mitral valve involvement has a good prognosis. To prevent bacterial endocarditis, antibiotic prophylaxis is used as it would be in other individuals with mitral valve prolapse. A prospective study of 70 patients with Marfan syndrome found that 21% of the patients developed ventricular ectopy and the patients with ectopy had a greater prevalence of mitral valve prolapse and left ventricular dilatation. Supraventricular and ventricular dysrhythmias may occur as primary dysfunctions.

**MEDICAL MANAGEMENT APPROACHES TO MARFAN SYNDROME**

There is no specific treatment for Marfan syndrome, but the cardiovascular complications generally respond to medical treatment in the early to mid stages of the disease. Proper management of the patient with Marfan syndrome depends on early recognition of the diagnosis and the identification of cardiovascular problems. Regular echocardiograms should be done to assess aortic dimensions. Leggett et al. found that an aortic ratio (observed dimension divided by predicted dimension based on age and body surface area) ≥1.3 or a change in aortic ratio >5% per year is predictive of a high risk of complications.

Tensile and shear stress from blood rushing through the ascending aorta make the risk of aortic dilatation and dissection high. Beta-blockers and calcium channel blockers are used to reduce the contractility of the heart and decrease the heart rate. This is thought to diminish the stresses to the aortic root and arch. If beta blockers are not tolerated, blood pressure could be lowered by angiotensin-converting enzyme inhibitors or calcium antagonists which decrease peripheral resistance to blood flow. Compliance with the medication regimen is good (80%) but in a cohort study, 20% admitted to skipping a dose of medicine more than once a month.

Aortic root replacement or reconstruction is used when the dilatation reaches ≥ 5 to 5.5 cm. Earlier surgical intervention should be considered if there is a familial history of aortic dissection, severe aortic or mitral regurgitation, need for other major surgery, or in planning for pregnancy. Aortic root surgical interventions that do not involve replacement of the patient's own aortic valve are beneficial to avoid life-long anticoagulation therapy. If there is dissection of the aortic root, a composite graft repair is the procedure of choice.

Patients with Marfan syndrome and their families should be counseled regarding the hereditary nature of the disease (autosomal dominant transmission), the prognosis, and the changes in lifestyle that may be necessary. Musculoskeletal manifestations of Marfan syndrome may also require surgical intervention; however, surgery for scoliosis may be contraindicated in patients with severe cardiovascular compromise. Severe pectus excavatum may present a problem for surgical incisions for cardiac and aortic repair.

Pregnancy involves special considerations for the woman with Marfan syndrome as peripartum complications may or may not occur. Peripartum complications, due to increased hemodynamic stresses, include aortic dissection, postpartum hemorrhage, or death. The risk of dissection is particularly heightened during the third trimester, parturition, and the first postpartum month. Regular echocardiographic monitoring should be done during pregnancy. Beta blockers should be prescribed at least from the second trimester onward to reduce risks; however, there may be adverse effects to the fetus from the beta blockers. These adverse effects include intraventricular growth retardation, bradycardia, hyperbilirubinemia, hypoglycemia, and apnea post delivery. A high risk of miscarriage or premature delivery exists in the presence of aortic changes. Good tolerance of pregnancy usually occurs in women with an aortic root diameter less than 4 cm. Women with Marfan syndrome have a 50% risk of giving birth to a child with the disease.

**SCIENTIFIC EVIDENCE SUPPORTING THE NEED FOR EXERCISE TRAINING IN PATIENTS WITH MARFAN SYNDROME**

Although there are numerous reports that recommend specific limitations of exercise for individuals with Marfan syndrome, there are few controlled studies on the effects of exercise in these individuals. A small exercise testing study of 17 young adults with Marfan syndrome, compared pulmonary function through spirometry, peak oxygen uptake measured during a bicycle ergometer test, and peak torque generated during isokinetic knee testing with expected norms of a healthy population. The individ-
ials having the disease were found to have a 30% to 50% reduction in peak oxygen uptake compared to untrained control values even though echocardiography did not indicate insufficient cardiac pump capacity. Furthermore, the ECG did not show abnormalities on those individuals that finished the test, and peak heart rate and diastolic blood pressure of those not on beta-blockers was comparable to expected norms. Other cardiovascular system abnormalities such as changes in elastic fibers of blood vessels that diminish blood distribution to the muscles and deconditioning were suggested as the limiting factors in exercise capacity. Impaired pulmonary function was not believed to contribute to diminished work capacity because spirometric tests did not indicate any pulmonary limitations during exercise. However, subjects with Marfan syndrome had mean total vital capacity 30% greater than mean predicted values of the normal population and residual volume twice as high as expected for predicted values of the normal population. The ratio of residual volume to total vital capacity was approximately 40%, and in the normal population, it is only 25%. The authors suggest that these differences could be interpreted as decreased elasticity of the lung tissue. Females with Marfan syndrome demonstrated decreased knee flexion torque than controls at the higher speed tested in an isokinetic test of knee flexion/extension strength. The difference in muscle strength was thought to be due to connective tissue changes that were detected only at the higher speed. The authors cited a number of research articles with exercise recommendations for individuals with Marfan syndrome, including that by Braverman, but overall felt that individuals with Marfan syndrome could benefit from physical training provided they used some precautions. This study supports the use of closely monitored bicycle ergometry exercise testing as a safe method to detect exercise response in individuals with Marfan syndrome that do not have an aortic diameter greater than 5 cm or dissection of the aorta. However, additional studies using more subjects and studying subjects over time are needed to aid the clinician in determining the type of testing and exercise intensity that would be appropriate for individuals with Marfan syndrome.

GUIDELINES FOR EXERCISE TRAINING IN PATIENTS WITH MARFAN SYNDROME

Advances in medicine, technology, and pharmacology have significantly altered the disease management of Marfan syndrome. Likewise, there is growing interest in the use of exercise for individuals with chronic disease or disabilities. The primary goal of exercise programs is to optimize functional capacity regardless of the chronicity of the disease or course of the disease. Within any given population, there exists a wide range of exercise abilities determined by multiple factors such as progression of the disease, response to treatment, co-morbidities, and even mental outlook. Appropriate exercise programs in conjunction with sound medical management can yield improvements or at least prevent further deterioration. Exercise is often viewed as the most positive step in regaining some type of normal lifestyle. For those individuals, young or old, who have Marfan syndrome, appropriate exercise should be a major component of their medical management.

Exercise prescription is the cornerstone of any exercise program and includes: intensity, duration, frequency, type of exercise, and progression. The safety of an exercise prescription for an individual is best monitored by heart rate, electrocardiogram, blood pressure and the rate of perceived exertion. The exercise prescription must be individualized for each patient with Marfan syndrome since the response to exercise will differ between patients depending on disease progression, medical management and hemodynamic alterations. Low level or heart rate limited graded exercise testing, as opposed to maximal testing, is best in this population to assess functional capacity and hemodynamic responses without causing undue stress to the cardiovascular system.

If the patient is severely compromised, a simple walk test should provide enough information to use for the exercise prescription.

In a survey of individuals with Marfan syndrome, 84% of participants reported choosing their physical activities with Marfan syndrome in mind, and 79% modified their exercise based on having Marfan syndrome. Activities that were avoided included high impact sports, activities with rapid starts and stops, and isometric activities. The 3 activities chosen by the most respondents were walking, hiking, swimming, and bicycling. These activities are consistent with the recommendations of several reports. The studies suggest prohibiting collision/contact sports and isometric exercises because of the risk of aortic dilatation and dissection. Hypermobile joints are at increased risk of injury during collision or contact sports. Activities that require sudden acceleration and deceleration should also be avoided.

Use of dynamic exercise of low to moderate intensity can safely increase heart rate, stroke volume, and cardiac output while decreasing peripheral resistance. It is recommended that individuals with Marfan syndrome not exceed 50% of their aerobic capacity and not exceed a heart rate of 110 beats per minute (or no greater than 100 beats per minute if taking beta-blockers). Recommended sports and recreational activities include: golf, rifflery, bowling, billiards, walking, modest hiking, skating (not hockey), snorkeling, noncompetitive doubles tennis, and bicycling. Lap swimming is not a recommended activity because it is classified as a high dynamic component activity requiring >70% maximal oxygen uptake. Individuals with Marfan syndrome should avoid exercising at high altitudes and scuba diving because of the change in atmospheric pressure that can cause spontaneous pneumothorax. Extreme sports, exercises that require progressive levels of exertion during training (those designed to maximize aerobic work capacity), and exercise in environmental extremes are also to be avoided. Because of the unpredictability of physical demand in extreme sports,
it is difficult to regulate heart rate and blood pressure safely. Exercise in environmental extremes of temperature or humidity carry risks associated with changes in blood volume, electrolytes, and hydration. Working above an aerobic capacity of 50% may cause undue stress to the cardiovascular system.

CONCLUSION
Although significant risks of aortic dilatation and dissection in patients with Marfan syndrome exist, there are a number of physical activities in which patients can safely participate to maintain health and well-being. Current level of fitness can safely be determined via bicycle ergometer testing, as long as the aortic diameter is less than 5 cm as measured by echocardiography. Caution should be used in testing by carefully monitoring the electrocardiogram and the patient. Generally, low to moderate intensity exercise, avoiding sudden bursts of activity or isometric activity are the safest. However, extra caution should be used for patients with Marfan syndrome that have undergone aortic root replacement. Physical activity must be even further limited. Consideration should be made for avoiding any exercise that substantially elevates heart rate or blood pressure. Each patient should be considered individually, weighing the risks and benefits of exercise.

CASE REPORT: EXERCISE PRESCRIPTION FOR A PATIENT WITH MARFAN SYNDROME
A 17-year-old male was referred to physical therapy (PT) with complaints of right shoulder pain for 1 week, and of difficulty standing erect for >5 to 10 minutes. The patient was 4 weeks post spinal fusion with Harrington rods to correct a 51° scoliosis. The patient complained of difficulty sleeping because of shoulder pain and limited walking because of difficulty standing erect. He was receiving homebound school instruction.

Medical history:
Marfan syndrome, aortic root replacement 6 months prior to referral to PT, dislocated lenses, frequent chiropractic care for neck pain
Family history:
Unspecified heart problems, diabetes mellitus in grandparents
Allergies:
No known allergies
Medications/supplements:
Atenolol, multi-vitamin, iron (post-op)
Diagnostic testing:
None since MRI of spine, ECG and echocardiogram preoperatively; the specific results of the tests were not known by the parent, but were reported as “OK”
Social:
Lives with parents in 2 story home; plays drums, guitar, and piano; denies smoking or drinking alcohol

Examination:
- Anthropometrics: 6’5” tall
- Posture: forward head and shoulders, flat lumbar spine, “pigeon chest,” atrophy of shoulder and hip girdle musculature
- Active range of motion (AROM): Within normal limits (WNL) upper extremities and lower extremities except bilateral (B) shoulder abduction to 90° and limited by pain; hand behind back to waist on the right (R), to scapula on the left (L); complains of shoulder pain with abduction and horizontal adduction with elevation
- PROM: WNL
- Neurological screen: WNL
- Joint mobility: hypermobile extremity joints noted by hyperextension/recurvatum of elbow, knee, metacarpophalangeal joints on AROM
- Transfers: requires minimal assist for sit to/from supine
- Gait: within functional limits (WFL), but flexed forward at hips
- Skin integrity: incision over spine with a few steri-strips intact and small scabs at mid thoracic area, no signs of infection, no drainage; well healed scar over sternum
- Positive impingement tests of the right shoulder including passive flexion with overpressure, Hawkins-Kennedy test and Speed’s test

Assessment:
Right shoulder impingement syndrome, proximal limb weakness, postural dysfunction, deconditioning, disuse atrophy
The patient fits into the following American Physical Therapy Association’s Guide to Physical Therapist Practice patterns:
- 4B Impaired posture
- 4C Impaired muscle performance
- 4E Impaired joint mobility, motor function, muscular performance, and range of motion associated with localized inflammation
- 4F Impaired joint mobility, motor function, muscle performance, range of motion, and reflex integrity associated with spinal disorders
- 6B Impaired aerobic capacity/endurance associated with deconditioning

Outcome
The patient’s right shoulder impingement improved within 3 weeks. He no longer had pain, his ROM was equal to the uninvolved side, and the impingement tests were negative. He was sleeping through the night without waking due to shoulder pain. Right shoulder strength had improved to 4/5. He was able to walk ½ to ¾ of a mile before his back ‘felt tired.’ Hip strength was 4/5 bilaterally.
### Exercise Prescription:

<table>
<thead>
<tr>
<th>MODE</th>
<th>GOALS</th>
<th>INTENSITY</th>
<th>FREQUENCY</th>
<th>DURATION</th>
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<tbody>
<tr>
<td>Strengthening</td>
<td>- Improve shoulder girdle strength to 5/5 to decrease impingement</td>
<td>- Light dynamic resistance (approximately 50% of 1 rep maximum)</td>
<td>3 times per week</td>
<td>4-6 months (anticipate impingement to improve in 4-6 weeks)</td>
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<tr>
<td></td>
<td>- Improve hip strength to 5/5 to improve walking posture</td>
<td>- Exercise bands for upper extremity strengthening</td>
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<td>- Limb weight/body weight for lower extremities</td>
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<td></td>
<td>- High repetitions</td>
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<td></td>
<td>- NO ISOMETRICS</td>
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<tr>
<td>Aerobic</td>
<td>Improve stamina/endurance for return to school by using large muscle groups for exercises</td>
<td>Light intensity (Borg scale 8-11)</td>
<td>4-5 times per week</td>
<td>Anticipate 6 weeks to tolerate full day of school without fatigue</td>
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<tr>
<td>(preferred activities include walking and exercise bicycle)</td>
<td>[See note 3 below]</td>
<td>[See note 3 below]</td>
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</table>

**Note 1.** Shoulder exercises of flexion, scaption, abduction, external rotation, horizontal abduction, horizontal adduction, extension, adduction and internal rotation, rowing and hip exercise of extension with and without the knee flexed, abduction, external rotation, adduction, flexion and internal rotation, bridging, squats, lunges.

**Note 2.** Avoiding isometric strengthening exercises reduced the stress to the patient's cardiovascular system.

**Note 3.** Heart rate would not be utilized to monitor intensity as this patient is taking a beta-blocker.

The patient and his mother chose to discontinue physical therapy at that time as he was planning to return to school in 2 weeks. He was instructed to continue with his exercise program and to call the physical therapist with any questions or concerns. Follow-up by telephone, 3 weeks later, revealed that the patient was able to return to school full days, but complained of fatigue at the end of the day.

It was important for the physical therapist to consider that this patient had Marfan syndrome when planning treatment in order to avoid unnecessary stresses to the cardiovascular system which would have occurred with isometric or plyometric exercise. Determining the correct intensity for aerobic exercise to improve endurance needed to be done by use of the Borg rate of perceived exertion scale rather than heart rate because of the use of beta blockers in this patient. Stretching and joint mobilization to increase range of motion were avoided due to capsuloligamentous laxity and the absence of range of motion restrictions with passive testing.

### REFERENCES


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