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Physical Therapy Management for an Adolescent with Loeys-Deitz Syndrome (LDS): A Case Report

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Abstract

Background: Loeys-Dietz Syndrome (LDS) is a rare heritable connective tissue disorder characterized by aortic root aneurysm, arterial tortuosity, hypertelorism, and uvular anomalies. Signs and symptoms vary widely, and overlap considerably with Marfan Syndrome, Ehlers-Danlos Syndrome vascular-type, and Shprintzen Goldberg syndrome. Evidence is sparse to guide optimal physical therapy management for individuals with LDS. The purpose of this case report is to highlight the clinical decision making regarding physical therapy management for an adolescent with LDS. It also is to increase awareness and understanding of LDS. **Case Description:** A 14 year old male recently diagnosed with LDS presented to an outpatient physical therapy clinic per physician referral to improve shoulder and general joint stability. The patient demonstrated generalized joint hypermobility and muscle weakness, minimal functional impairment, and no pain. **Intervention:** A low to moderate intensity whole-body home exercise program with static and dynamic components was prescribed 3-4 times per week over 4 session, and a lifestyle of low to moderate intensity aerobic exercise was encouraged. No adverse events were reported. **Discussion:** Clinicians are cautious to prescribe moderate to high intensity static or dynamic exercise, and sports participation, for patients with thoracic aortic disease (TAD). High-quality evidence to support this is lacking; however, these activities should be avoided due to theoretical concerns of increasing risk of aortic dissection in this population. Clinical recommendations include educating about the risks and benefits of exercise and sports participation, and disseminating current evidence and guidelines, to empower patients and families to make informed decisions.

Keywords: Physical therapy, exercise prescription, Loeys-Dietz Syndrome, thoracic aortic disease, heritable connective tissue disorders, aortic root aneurysm.

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Background

More than 200 heritable diseases affecting connective tissue have been described. These disorders are the result of genetic abnormalities that disrupt supportive structures between the cells of the body such as collagen, elastin, and ground substance. Many tissues and organs can be involved, including skin, bones, joints, heart, blood vessels, lungs, eyes, and ears. Common types of heritable connective tissue disorders include Ehlers-Danlos Syndrome (EDS), Epidermolysis bullosa, Marfan Syndrome (MFS), and Osteogenesis imperfecta.[1] A recently discovered heritable connective tissue disorder, Loeys-Dietz Syndrome (LDS), was first described by Dr. Bart Loeys and Dr. Hal Dietz at the Johns Hopkins University School of Medicine in 2005.[2]

LDS is an autosomal dominant genetic disorder caused by one of five genetic mutations that encode for receptors involved in the Transforming growth factor beta (TGFβ) signaling pathway.[3] LDS type one results from a mutation of the TGFβ receptor one (TGFβR1) subunit, and type 2 from a mutation of TGFβ receptor two (TGFβR2) subunit. LDS type three is the product of a mutation of the mothers against decapentaplegic homolog three (SMAD3) gene. LDS type four results from a mutation of TGFβ ligand 2 (TGFβ2), and type five from a mutation of TGFβ ligand 3 (TGFβ3). LDS most frequently results from mutations in the genes encoding for TGFβR1 and TGFβR2.[2] Interestingly, these mutations have been predicted to result in a loss of subunit function, yet paradoxically lead to an increase in in TGFβ pathway signaling.

LDS clinically presents itself in a multitude of ways, but four primary characteristics have been identified.[3] These include: aneurysms, arterial tortuosity (twisting and winding of arteries), hypertelorism (widely-spaced eyes), and a bifid or broad uvula. Of these, the most prominent findings are aneurysms, most commonly located at the aortic root (most proximal to the heart). Aneurysms within the aorta are a risk for aortic dissection, rupture, and sudden death. Dissections have been reported in patients as young as six months. Arterial tortuosity, which is not harmful medically, is the most common finding of LDS (92% of cases), and is primarily found in the head and neck vasculature.[2, 3] Other possible symptoms of LDS affect a wide range of body systems, including craniofacial, skeletal, integumentary, cardiovascular, ocular, immune, and others (Table 1).[2, 3] Symptoms of interest regarding physical

Table 1. LDS Symptoms

Body System	Possible Symptoms
Cardiovascular	*aortic root aneurysm**, *arterial tortuosity**, patent ductus arteriosus (PDA), atrial/ventricular septal defect (ASD/VSD), bicuspid aortic valve (BAV), mitral valve prolapse (MVP)
Craniofacial	*hypertelorism (widely spaced eyes)**, *bifid or broad uvula**, malar hypoplasia (flat cheek bones), craniosynostosis (early fusion of skull bones) blue sclerae, small or receding chin
Skeletal	clubfoot, scoliosis or kyphosis, cervical spine instability or malformation, joint laxity, pectus excavatum or carinatum, OA, spondylolisthesis, Congenital hip dysplasia, recurrent subluxations, finger contractures, osteoporosis, arachnodactyly (long digits)
Integumentary	translucent skin, soft or velvety skin, easy bruising, abnormal or wide scarring, hernias
Ocular	myopia (nearsightedness), retinal detachment, strabismus (improper eye alignment)
Other	food or environmental allergies, GI inflammatory disease, spontaneous rupture of uterus, spleen, or intestines; dural ectasia.

**primary symptom*

(Van Laer et. al, 2014), (Loeys-Dietz Foundation, 2019)

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therapy management include aortic root aneurysm, congenital heart conditions, clubfoot, scoliosis or kyphosis, cervical spine instability or malformation, joint laxity, pectus deformity, osteoarthritis (OA), osteoporosis, spondylolisthesis, congenital hip dysplasia, recurrent subluxations, finger contractures, and bruising easily.

There is considerable overlap in symptoms between the five types of LDS, and between LDS and other heritable connective tissue disorders; however differences do exist. SMAD3 mutations (LDS3) have been associated with aneurysms osteoarthritis syndrome, which has strong clinical similarities to LDS but the presence of early onset OA. TGFβR2 mutations (LDS2) produce an LDS-like phenotype but without aortic disease.[2] Other genetic connective tissue disorders with similar symptoms include MFS, EDS vascular type, and Shprintzen-Goldberg syndrome. Marfan syndrome is caused by a mutation of the fibrillin-1 protein (FBN-1), and shares features with LDS including aortic dilation and aneurysm with possible dissection, mitral valve prolapse (MVP), pectus deformities, scoliosis, kyphosis, joint laxity, pes planus, arachnodactyly, and dural ectasia.[2-4] However, aortic dissection is more likely to occur at smaller diameters in individuals with LDS. Furthermore, aortic disease is significantly more widespread in LDS, potentially involving aortic side branches and the cerebral circulation.[2] EDS has six types resulting from a mutation of fibrillar collagen type I, III, or V. The vascular type most similarly resembles LDS with arterial or organ rupture, easy bruising, translucent skin, and common EDS symptoms such as joint hypermobility and generalized tissue fragility.[5] Shprintzen-Goldberg syndrome, like LDS, has symptoms including aortic root dilation, craniosynostosis, pes planus, pectus deformity, scoliosis, and joint hypermobility, but is more likely to involve intellectual disability and delayed development, with milder cardiac abnormalities.[6]

Diagnostic criteria for LDS have not been clearly established, but clinical diagnoses are made based on family history, a physical examination, genetic testing, and arterial imaging. TGFBR1/2 genetic testing should be considered in patients who have symptoms of LDS, those with an MFS-like presentation that do not fulfill MFS criteria, those with a vascular EDS presentation with normal type III collagen, families with autosomal dominant thoracic aortic aneurysms, and in persons who are the sole member of their family with aortic root dilation or dissection. It is likely that there are people with LDS who have been falsely diagnosed with another similar connective tissue disorder, making it difficult to determine the prevalence of the condition.[7] Arterial imaging, including a CT angiogram (CTA) and MR angiogram (MRA), is recommended for the head, neck, chest, pelvis, and abdomen to detect for aneurysms across the entire arterial tree. To detect for arterial tortuosity, 3D CTAs or MRAs are recommended. However, these tests are more for diagnostic purposes rather than out of medical necessity because arterial tortuosity is benign. [2] Around two-thirds of LDS cases are the product of spontaneous mutations, which tend to have more severe craniofacial and orthopedic findings, while one-third have a familial link.[2]

Treatment options for LDS include medications, regular arterial imaging, exercise restrictions, and bracing. In more progressed cases, cardiovascular or orthopedic surgery may be indicated. Medications are used to lower heart rate and blood pressure to decrease the risk and growth of aneurysms, and may be used to treat disease-related allergies. Annual aortic echocardiograms are essential to monitor formation of aneurysms and detect dissections, with the frequency of testing dependent upon aneurysm size and growth rate. Imaging of the cervical spine to assess for abnormalities or instability can be performed, but rarely is surgical correction needed.[3] Vascular surgery, most commonly aortic root replacement, is indicated for individuals with rapidly enlarging aortas or significant family history of arterial dissection. Fortunately, aortic root replacements have a high success rate.[3] For orthopedic issues, bracing or surgical management may be warranted. Orthoses can be beneficial for management of scoliosis, club foot, pes planus, and congenital hip dysplasia. Orthopedic surgery can be selected to correct pectus deformities, but are done primarily for aesthetic purposes rather than preventing or resolving medical complications.[3]

Exercise restrictions are recommended for LDS patients as another way to slow aneurysm formation and growth. These recommendations include avoiding competitive sports, especially contact sports, and any activities or exercises involving exhaustive muscle straining, such as push-ups, sit-ups,

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and chin-ups. However, light to moderate aerobic exercise that can be performed while maintaining a conversation is suggested for individuals with LDS. Hiking, cycling, jogging and swimming fit into this category, and are known to help lower heart rate and blood pressure.[3] Furthermore, the American Heart Association (AHA) and American College of Cardiology (ACC) collaborated to create a grading system to classify the intensity of competitive sports to aide in making participation recommendations for athletes with cardiac abnormalities. Peak static and dynamic components achieved during competition form the basis of the classifications. The static component relates to an estimate of max voluntary contraction achieved, and positively correlates with an increased blood pressure. The dynamic component is related to the estimated maximal oxygen uptake (VO2 max) experienced in sport, and positively correlates with cardiac output. The classification ranges from low static and dynamic class IA sports which includes bowling, golf, and yoga, to high static and dynamic class IIIC sports which include boxing, rowing, cycling, and triathlon.[8] For athletes with LDS and vascular EDS, participation in class IA sports is reasonable if there is no presence of: aortic enlargement (aortic root z-score >2) or dissection, branch vessel enlargement, moderate to severe mitral regurgitation, or extracardiac organ system involvement that makes participation hazardous. These sports include cricket, curling, riflery, bowling, golf, and yoga. Moreover, participation in any competitive sport that involves intense physical exertion or potential for bodily collision is not recommended. However, strength of these recommendations are low as they are based on findings from randomized or nonrandomized studies with methodological limitations, or from expert opinion.[9]

The lack of high-quality evidence to support exercise prescription and sports participation in patients with TAD , as well as a dearth of evidence about the effects of physical rehabilitation in this population, make it unclear how a physical therapist can optimally evaluate and treat patients with LDS. The purpose of this case report is to highlight the clinical decision making regarding physical therapy management for an adolescent with LDS. It also is to increase awareness and understanding of LDS, a recently discovered uncommon connective tissue disorder.

Case Description

The patient is a 14 year old Caucasian male who presented with his father to an outpatient private practice physical therapy clinic in the Midwest. The patient had been seen one week prior at a nearby tertiary care center for a follow-up appointment regarding scoliosis, and also underwent genetic testing. After the results were obtained, his physician diagnosed him with Loeys-Dietz Syndrome and referred him to physical therapy for exercises to improve joint stability, particularly of the shoulder. The patient reported no complaints of pain or functional limitations. The patient was not wearing a spinal orthotic at the time, but reported that he wears one 14 hours each day by physician order. The severity of scoliosis was not determined, but it can be assumed that the curve was >25 degrees, as that is the general minimum criteria for effective orthotic bracing for scoliosis.[10]

The patient reported medical history including aortic dilation and mitral valve prolapse (MVP) that were being treated with beta blocker medications and monitored regularly with arterial imaging. Interestingly, the patient's father reported that he also has LDS, being diagnosed at age 32. Moreover, the father reported that 20-30 of their family members also have the condition, and that the patient's aunt had passed away from LDS complications. Recreationally, the patient reported enjoying videogames and spending time with friends. Goals were made collectively between the patient and father and included improving general strength and preventing complications.

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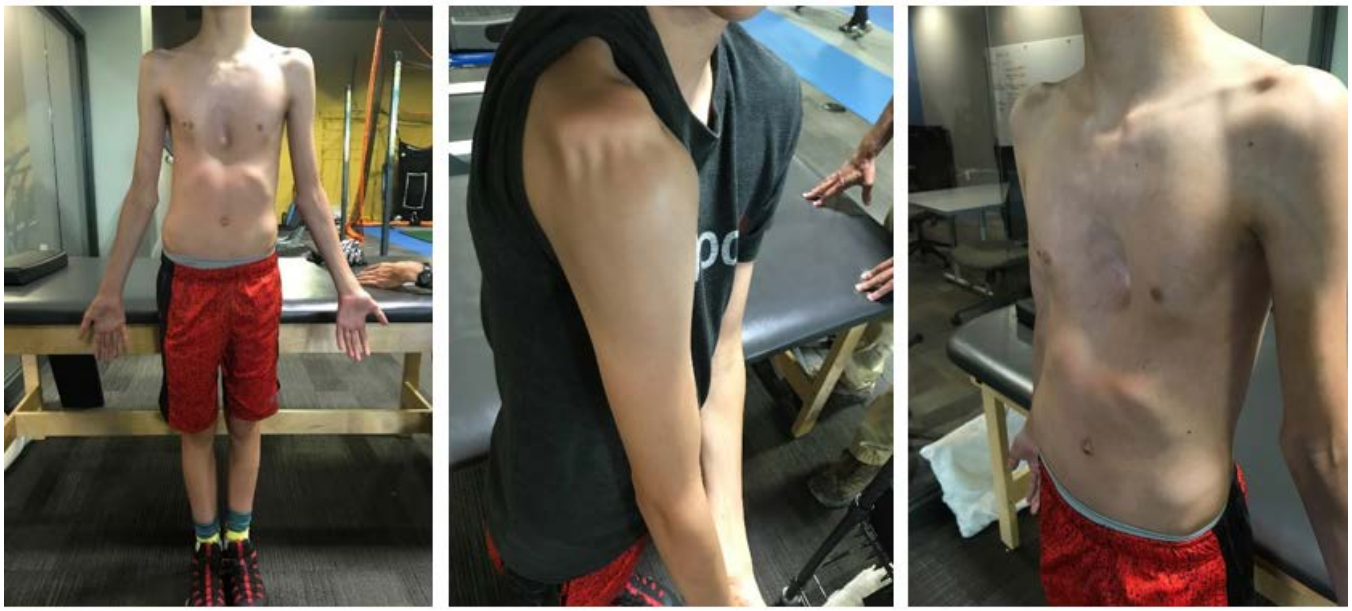
Examination & Evaluation

On observation, the patient demonstrated a tall and thin ectomorphic body type with little muscle mass**,** large feet, and a receding chin (Figure 1A). During the subjective interview, the patient demonstrated the ability to passively create a grade +3 (>2cm) glenohumeral sulcus sign in both arms by pulling down on his arm with his opposite hand (Figure 1B). He denied pain when doing this, and denied any past shoulder subluxations or dislocations. The patient removed his shirt to reveal a severe pectus excavatum deformity that his father reported was one centimeter away from his thoracic vertebrae (Figure 1C). The patient denied any past or current chest pain or difficulty breathing at rest or with activity.

Figure 1. Patient Clinical Presentation

A. Ectomorphic body type **B**. Sulcus Sign **C**. Pectus Excavatum



As an assessment of whole body functional movement, the selective functional movement assessment (SFMA) was used. The SFMA consists of 15 functional movements designed to assess fundamental movement patterns in individuals with musculoskeletal pain.[11] Functional movements regarding upper body include cervical flexion, extension, and rotation, shoulder medial rotation with extension (upper extremity pattern 1), and shoulder lateral rotation with flexion (upper extremity pattern 2). Functional movements regarding trunk and lower body include multi-segmental flexion, extension, and rotation, overhead deep squat, and single limb balance where the patient's opposite hip is flexed to 90 degrees. SFMA movements are qualitatively scored into one of four categories: functional nonpainful (FN), functional painful (FP), dysfunctional nonpainful (DN), and dysfunctional painful (DP). A movement is deemed functional based on meeting specific criteria for range of motion (ROM) and dynamic muscular control. A movement is scored painful based on the subjective report of pain during the movement. Inter-rater reliability for SFMA scoring has been shown to be moderate to good.[11] SFMA classifications can help physical rehabilitation professionals identify holistic movement impairments and aide in guidance of treatment. The patient did not experience pain during any movement, and was functional for all besides overhead deep squat and single limb balance. During overhead deep squat, significant bilateral dynamic genuvalgum was present, and during single limb balance the patient demonstrated contralateral hip drop and was unable to hold for 10 seconds without a corrective step for either extremity.

Additionally, the patient demonstrated active ROM beyond the SFMA criteria for full active ROM on all items, which was deemed as generalized hypermobility. The Beighton instrument is a validated test

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to determine generalized joint mobility in children six to twelve years, however was not used in this case.[12] It is unclear whether Beighton scores would remain valid for our 14 year old patient as he was likely experiencing significant body composition changes as a result of puberty that may alter global joint mobility, whereas most 6-12 year old boys would not be expected to. Regardless, the clinical utility of obtaining Beighton scores to determine generalized joint hypermobility in our case would have been low, as they would be unlikely to change the plan of care in light of the SFMA ROM observations and positive bilateral sulcus signs.

On strength testing using manual muscle testing (MMT), the patient demonstrated ability to hold against moderate to maximum resistance (4+/5) for shoulder abduction and internal rotation, moderate resistance (4/5) for shoulder external rotation, mild resistance (3+/5) for shoulder flexion, middle trapezius, and rhomboids, and was unable to hold against resistance but demonstrated full active range of motion (3/5) for lower trapezius. A comprehensive evaluation of MMT to determine strength, including cervical, distal forearm, and lower extremity musculature, could have been conducted, but would have been of little clinical utility based on the dynamic hip, knee, and core instability demonstrated by the patient during SFMA functional deep squat and single limb balance movements. Furthermore, the use of MMT to determine strength for patients with TAD is of questionable safety. This is because MMT subjects patients to repetitive high-force isometric loads that acutely raise blood pressure, and is concerning for exacerbating aortic dilation or aneurysms.

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The Quick Disabilities of Arm, Shoulder, & Hand (QuickDASH) patient-reported outcome measure was completed by the patient to assess and monitor physical function of the upper extremity and related symptoms over the course of the physical therapy episode. The QuickDASH extracts 11 of the 30 items from the original DASH, and highly correlates to the full-length measure. Items include the amount of difficulty to perform ADLs, sleep, work, and recreational and social activities due to symptoms, and has patients rate the severity of symptoms in the past week. Like the DASH, the QuickDASH scores range from 0, representing no disability, to 100, indicating most severe disability. For upper extremity musculoskeletal disorders, the minimal detectable change (MDC) is reported between 11-17.2 points, and the minimal clinically important difference (MCID) is between 9.0-11.3 points.[13] The patient scored a 2.3/100, demonstrating 2.3% functional impairment. A summary of clinical findings during the initial evaluation can be found in Table 2.

Table 2. Initial Evaluation Summary of Findings

SFMA	Active Cervical Flexion	FN	
	Active Cervical Extension	FN	
	Cervical Rotation	Left FN	Right FN
	Upper Extremity Pattern 1 (MRE)	Left FN	Right FN
	Upper Extremity Pattern 2 (LRF)	Left FN	Right FN
	Multi-Segmental Flexion	FN	
	Multi-Segmental Extension	FN	
	Multi-Segmental Rotation	Left FN	Right FN
	Single-Leg Stance	Left DN	Right DN
	Overhead Deep Squat	DN	
Manual Muscle Testing	Motion	Left	Right
	Shoulder Flexion	3+/5	3+/5
	Shoulder Abduction	4+/5	4+/5
	Shoulder External Rotation	4/5	4/5
	Shoulder Internal Rotation	4+/5	4+/5
	Rhomboids	3+/5	3+/5
	Middle Trapezius	3+/5	3+/5
	Lower Trapezius	3/5	3/5
Special Testing	Sulcus Sign (arm at side)	Left 3+	Right 3+
Functional Measures	QuickDASH	2.3/100	

FN: functional nonpainful, DN: dysfunctional nonpainful

Clinical Impression

The patient denied pain or functional limitation, and minimal functional impairment was found based on the QuickDASH score. The patient demonstrated generalized joint hypermobility, especially within the glenohumeral joint as shown by bilateral positive sulcus signs. This was concerning for glenohumeral joint subluxations or dislocations, despite the patient denying any such events in the past. Gross scapulohumeral and lower extremity strength were poor based on manual muscle testing and presence of significant dynamic instability of knees, hips, and core with squatting and single limb balance. No pain was reported throughout the exam. Significant components of the subjective history included a history of cardiac abnormalities including aortic dilation and MVP, and a prominent family history of LDS. Patient and family goals included improving general strength and preventing future complications.

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Intervention

Based on the clinical similarities between the presentation of the patient and individuals with Ehlers-Danlos Syndrome, along with the patient and family goals, level one EDS exercises from the MedBridge® home exercise program website were taught to the patient and prescribed as a home program. These included six low-level general hip and core exercises, including: supine posterior pelvic tilts, double leg bridges, supine marching, prone hip extension, hook lying adductor ball squeeze isometrics, and hook lying clam shells with elastic band resistance. Additionally, standing shoulder external rotation with elastic band resistance was given to improve glenohumeral joint stability. The patient was instructed in and demonstrated proper form of each exercise, and reported low to moderate fatigue immediately after exercises. Poor muscular activation and endurance of core musculature was noted as the patient had difficulty initiating and maintain a posterior pelvic during the double leg bridge exercise. The patient was instructed to complete three sets of ten repetitions for all exercises three to four times per week. A plan of care was discussed with the patient and his father to schedule one time per week for three to four weeks to review, modify, and progress or add exercises as needed to establish an optimal home exercise program (HEP), with the goal of independence and adherence for long-term strengthening.

Ongoing Management

The patient returned for three follow-up appointments after the initial visit, all spaced one week apart. Between the time of the first and second visit, information about LDS was sought out in the literature to help determine the best course of action for physical therapy management for the patient. After becoming informed of this unique diagnosis, the focus of the second session was about educating the patient and family about exercise and activity participation guidelines for patients with TAD, as well as reviewing, modifying, and progressing exercises as appropriate. At the beginning of the session, the patient reported no pain or functional complaints currently, or in the past week. Because the patient reported having aortic dilation and MVP, a blood pressure was assessed at rest prior to the initiation of exercises. A value of 110/78mmHg was recorded, which is within the normal range. The patient also reported that his father did not send him the pictures of his HEP so he did not perform them the previous week. It was unclear whether this was the primary reason for non-adherence to the home program, or if it was apathetic patient behavior. Regardless, inter-family communication and home exercise program adherence was encouraged. Furthermore, this raised concern for continuous HEP adherence issues, and it was questioned whether the exercises could be made more challenging or interesting to help combat the issue. Therefore, after exercises were reviewed to ensure proper technique, supine and prone exercises, besides double leg bridges, were progressed to more challenging quadruped or standing exercises. Education was provided about avoiding high intensity and straining exercise and activities to decrease risk of cardiovascular complications. Encouragement towards a lifestyle of regular low to moderate intensity aerobic activity, such as leisurely biking and swimming, was also advised for long-term health benefits.

We did not assess the patient's blood pressure after completing exercises, but this could have been done. However, the patient did not demonstrate any signs or symptoms of significant fatigue during or immediately after exercise. Additionally, inquiries toward and more thorough inspection of the patient to determine the presence of other common LDS symptoms was not performed. Information that was not obtained that had the potential to alter the plan of care include presence of: congenital hip dysplasia, OA, osteoporosis, and cervical spine malformation. However, it is expected that the patient's father would be aware of and willingly offer this information, and that patient would have pain if OA was present.

During the third visit, the patient reported completing the HEP four times, and that he had participated in leisurely biking and swimming the previous week. In light of that, the goal for the session was to modify the HEP to keep the patient optimally challenged and engaged. In effort to do so, a circuit workout approach was selected. The circuit encompassed ten exercises, including seven new exercises, that continued to challenge all major muscle groups in both statically and dynamically, and

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were progressed to standing with a focus on functional movements. New exercises included: superman's (prone scapular retraction with arm lift at sides), non-impact form-running, squat chair touches with elastic resistance around thighs, shoulder flexed bent elbow weight carry, bent-elbow waist level weight carry, single leg balance (15 seconds each side), and modified burpees (non-impact). All exercises were designed to be moderate intensity, and thus a 30s on, 30s off work to rest ratio was selected. Ten exercises at this work-rest ratio made each circuit ten minutes. The patient was advised to complete two circuits with a five to ten minute rest interval between, four to five times per week. The patient was instructed in how to self-monitor heart rate using radial pulse as a way to objectively estimate and monitor exercise intensity and cardiac workload after each circuit was completed. The patient was educated to maintain heart rate below 100bpm during and after a circuit or bout of exercise for safety. This heart rate goal stemmed from recommendations given by the Marfan Foundation who advise patients with Marfan syndrome to exercise at or below 50% aerobic capacity, which on average is <110bpm. For patients on beta blockers, such as this patient, it is advised to keep heart rate below 100bpm.[14] Monitoring heart rate over blood pressure throughout and after exercise was selected due to efficiency and allowed the patient to be self-sufficient in estimating cardiac workload, as a blood pressure cuff and sphygmomanometer were not needed. The patients resting heart rate prior to circuit exercises was 72bpm. Immediately after the first circuit, heart rate was 88bpm. The patient rested for five minutes before the second circuit was initiated. After the second circuit, heart rate was 88bpm. The patient reported the circuits became "difficult" near the end, but did not report any signs or symptoms of pain or cardiorespiratory stress during and immediately after each circuit. Blood pressure was not recorded, but would have been if the patient reported signs or symptoms of significant cardiorespiratory stress, such as chest or shoulder pain, diaphoresis, lightheadedness, dizziness, or dyspnea.

During the fourth and final visit, the circuit workout was reduced to six exercises, and the weight carries were modified to be completed within his home. Additionally, the patient was given the option of continuing to complete the exercises as a circuit or to switch to traditional sets and reps. The QuickDASH was filled out by the patient and scored, resulting in a score of 2.3/100.

Outcomes

Outcome measures used to assess progress of this patient were few, but included monitoring for medically adverse events (e.g. injuries, dislocations, cardiovascular complications including aortic dissection/rupture, surgeries), HEP adherence, and changes in the upper extremity functional impairment via the QuickDASH. During the physical therapy episode, no complications were reported. HEP adherence was variable, with the patient completing all exercises between zero and four times per week. During the last visit, the patient admitted that he only came to therapy because his parents wanted him to. Despite efforts to make exercises more challenging and engaging, this response was not surprising as the patient did not have any pain or functional limitations, which are undoubtedly motivators for many patients receiving physical therapy treatment to adhere to a HEP. Pre and post QuickDASH scores did not change. This was not surprising based on the minimal functional impairment and lack of symptoms the patient began therapy with, as well as the short duration of the episode of care in which significant improvements in strength would not be expected.

Follow-up communication with the patient's father occurred via phone call three months after the end of the episode of care. The purpose of the follow-up was to monitor medically adverse events or recent surgical intervention, and HEP adherence. The patient and family were previously considering a Nuss bar placement to correct the pectus deformity, but had not chosen to do so. Additionally, overall HEP adherence was low, as the patient had little interest in the exercises and was hard to motivate per report of the father. No medically adverse events, including injuries, dislocations, or arterial or cardiac complications were reported.

Discussion

The purpose of this case report is to highlight the clinical decision making regarding physical therapy management for an adolescent with LDS. It is also to increase awareness and understanding

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of LDS, a recently discovered connective tissue disorder. The prevalence of LDS is unknown, but the diagnosis was recently first described, and is thus likely uncommon.[7] Accordingly, it is assumed that LDS is a rare condition for physical therapy professional in an outpatient orthopedic setting to encounter. However, it is valuable for physical therapy professionals to have a general understanding of the condition to safely and effectively prescribe exercise and offer appropriate advice regarding activity and sports participation when patients with LDS are encountered. Furthermore, patients with LDS commonly present with musculoskeletal problems such as joint laxity that physical therapy professionals are equipped to help improve.

Current physical activity recommendations lead the clinician to be cautious about prescribing more than moderate intensity exercise for patients with TAD; however, there is a dearth of high quality evidence to support them.[15] In 2019, Thijssen and colleagues published a review regarding exercise and sports participation in patients with TAD, including 38 studies. They found no evidence to support the theory that static exercise predisposes a person with TAD to acute aortic dissection more than dynamic exercise. Many of the studies evaluated were case reports with the majority of aortic dissections being related to weightlifting. However, these studies predominantly included patients under 20 years old, whereas a study of 650 people with a mean age of 62 years found that golf, regarded as a low static- and dynamic-component sport, was the sport most commonly associated with acute aortic dissection (32%). Following golf were swimming (16%), cycling (16%), weightlifting (12%), and dancing (8%). These studies highlight the importance of selection bias, as young people would be expected to partake in weightlifting at a higher rate and golf at a lower rate than older adults, and thus have higher reports of aortic dissections with these activities; yet these do not necessarily reflect that one activity has a higher risk of aortic dissection compared to the other. Additionally, Thijssen reported the overall incidence of sports-related acute aortic dissections in three retrospective cohort series varied widely, between four and 68 percent. Despite these findings, Thijssen and colleagues recommend avoiding heavy static exercises in patients with TAD due to the theoretical risk of increasing blood pressure and risk of aortic dissection. The authors also urge clinicians to avoid placing exercise and sports restrictions on TAD patients, but rather to explain both the positive and negative effects of exercise to patients with TAD in order to reached a shared understanding with the patient, and reduce physical activity-related fear and stress which may reduce quality of life. The authors concluded with a call for more randomized controlled trials that longitudinally evaluate the effect of exercise on thoracic aortic aneurysm dilation rate, the risk of TAD, quality of life, and survival of patients with TAD, as none are known to exist at this time.[15]

Regarding sport participation and training safety, multiple studies found that strength trained athletes had a slightly larger aortic diameter compared to dynamically-trained athletes, but that all mean aortic root measurements were below the threshold (>40mm) that likely demonstrates aortic pathology versus normal training adaptations.[15, 16] Athletes have been found to have larger absolute aortic diameters compared to controls, however differences are small.[15] Additionally, aortic size may be less a function of training and more of body size, as one study examining aortic root diameters found no significant difference between athletes and controls when body surface area (BSA) was controlled for.[17] The association between exercise and acute thoracic aortic dissections ranges widely (4-68%), and may be a result of differing definitions of what activities are ‘sport-related.’ One study included non-sports exertion and Valsalva maneuver-related activities such as lifting or moving heavy loads, sexual activity, and defecation, into the ‘sports-related’ category, while the other did not.[15]

Complimenting these findings are recent studies that shed hope for the positive effects of exercise in the context of aortic dilation. In one study, 17 middle-aged adults with MFS or LDS participated in a comprehensive and intensive three week inpatient rehabilitation program that included 30 minutes of daily bicycle ergometry, one hour of gymnastics four days per week, and one hour of fitness training and Nordic walking three days per week each. Outcomes included psychological distress based on questionnaires, medically adverse events, and physical fitness estimated by a combination of bicycle ergometry max power sustained over twenty consecutive minutes with a systolic blood pressure ≤160mmHg, and maximum Nordic walking distance. At the end of the three week program, physical

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fitness and psychological stress improved, and no adverse events, such as new cardiac arrhythmias or aortic complications, were observed. Furthermore, these effects carried over to the one year follow-up. Disappointingly, information about aortic diameters was not monitored.[18]

Furthermore, two controlled trials examining mice demonstrated positive results for exercise in aortic dilation in the setting of Marfan syndrome. Both studies included one or more mild to moderate intensity dynamic exercise training groups compared to a sedentary control group. A reduction in aortic diameter growth rate was observed in both studies, and aortic wall elasticity was improved in one study. Additionally, a training intensity level of 55-65% VO2 max was most beneficial for protective effects in the animal model, with higher intensity training weakening the effects.[15] In a randomized controlled trial of a related patient population, 140 patients with abdominal aortic aneurysms (AAA) were randomized into standard care or a rowing (isometric exercise) group. Both groups demonstrated similar abdominal aortic growth rates. Clinical utility of this study for patients with TAD is limited because of the differing etiology between TAD and AAA, and questionable validity of rowing as an 'isometric' exercise, but findings for the potential positive role of exercise in aortic dilation is encouraging.[19] Additionally, regular exercise has many known health benefits for adults with cardiometabolic conditions, such as reduced incidence of heart attack, stroke, hypertension, type two diabetes, and mortality.[20] In children and adolescents, exercise has been shown to improve cardiorespiratory and muscular fitness, cardiovascular risk factors, cognitive function, bone health, and weight status, and reduce symptoms of depression.[20] In contrast, strong evidence demonstrates that a sedentary lifestyle increases the risk of many adverse health conditions, such as coronary heart disease, stroke, metabolic syndrome, type two diabetes, breast and colon cancer, and shortens life expectancy.[21] Therefore, despite the risk of an acute aortic dissection during exercise in patients with TAD, the risk of an inactive lifestyle also ought to be considered when providing recommendations to patients and their families.

In this case study, a patient with LDS and known history of aortic dilation and MVP was prescribed low to moderate intensity exercise with mixed static and dynamic components three to four times per week over four weeks. No adverse events were reported at four weeks or at a three month follow up. No change in functional impairment was reported, but baseline impairment was low. Additionally, the short duration of the episode of physical therapy care, combined with overall low HEP adherence, was not conducive towards improving the patient's strength impairments. However, the patient and family were educated about how exercise can be safe for individuals with LDS, as well as equipped in how to do so with instruction in a properly dosed home exercise program. Furthermore, we hope this knowledge reduced any exercise participation fears and facilitated the adoption of a lifestyle of regular exercise, with the numerous associated health benefits.[20] The power of this case to inform appropriate exercise prescription and sport participation for patients with TAD is low due to the nature of case reports, questionable exercise adherence, follow-up data limited to three months, and the lack of objective outcome measures to assess aortic root diameter or other cardiovascular changes. At minimum, however, this report does not demonstrate any negative effects of low to moderate intensity mixed static and dynamic exercise for patients with LDS and TAD.

Clinical Recommendations

There is minimal evidence to guide the physical therapy professional in optimal management of patients with LDS. There is a need for randomized controlled trials evaluating the longitudinal effect of exercise on aortic dissection risk or survival in patients with TAD, as none are known to exist at this time. Therefore, in these clinical situations, professional judgement must be exercised. Based on information regarding similar connective tissue disorders and clinical judgement, the following guidelines are suggested for patients with LDS and TAD:

1) Treatments should be individualized based on patient impairments, activity limitations, participation restrictions, and goals.

2) Information should be obtained about the presence of cardiac and orthopedic conditions that cannot or may not be readily observable. These include congenital heart conditions and aneurysms

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beyond aortic root dilation, congenital hip dysplasia, osteoporosis, osteoarthritis, and cervical spine malformation.

3) On examination, inquire about and examine signs and symptoms of past or current cardiorespiratory distress such as aortic or arterial dissection; symptoms include sudden severe chest pain, pain migrating to chest, neck, back and abdomen, and/or an extremity; nausea/vomiting, dyspnea, and collapse. Inspect for orthopedic deformities such as pes planus, clubfoot, scoliosis/kyphosis, pectus deformity, and cervical spine malalignment.

4) Consider an alternative to MMT for assessing muscular strength to reduce repetitive acute bouts of increasing blood pressure and the subsequent undue cardiovascular stress. Alternatives to clinically estimate lower extremity strength include observing dynamic stability and alignment during movements such as double and single leg squats, single limb balance, and plyometrics. For the upper extremity, consider a similar approach to assessing ankle plantarflexion strength, where a low to moderate isotonic load is placed upon a muscle group over a high number of repetitions, such as a repeated dumbbell biceps curl; stop the test when the patient cannot achieve their full available active ROM. Although standardized data will not be available to formally assess strength this way, valuable clinical information can be obtained and recorded to measure progress throughout the episode of care. If MMT is chosen to assess strength, encourage the patient to breathe through the testing and avoid the Valsalva maneuver to avoid spiking blood pressure.

5) For exercise prescription, low to moderate intensity dynamic and/or static exercise is recommended to maximize health benefits, as evidence is lacking to demonstrate an increased cardiovascular risk of static exercise over the latter.[15] However, due to theoretical concerns, heavy static exercises should be avoided. Moderate intensity aerobic exercise can be attained by monitoring percent of max heart rate (64-76%), percent VO2 max (46-63%), rating of perceived exertion (12-13 on a 20-point scale, six on a 10-point scale), and by metabolic equivalent (MET) level (3.0-5.9).[22] In accordance with physical activity guidelines for Americans, patients with LDS should be encouraged to engage in moderate intensity aerobic exercise of 30 to 60 minutes per day, and complete strength training exercises including all major muscle groups two to three non-consecutive days per week for optimal health benefits.[22] However, unlike the guidelines, patients should stay within the low to moderate intensity exercise range, avoiding participation in vigorous exercise to decrease risk of adverse cardiovascular events.

6) For strength training, consider higher repetition (15-30) lower load (≤50% one-rep max) exercises to achieve a moderate intensity and reduce the chance of breath-holding. This exercise dosage is biased towards improving muscular endurance but will secondarily improve hypertrophy and strength with appropriate training volumes and frequency. Exercises should be performed within the mid-range of a patient's full ROM to reduce risk of joint dislocation, subluxation, and abnormal loading. Concentric, eccentric, and isometric exercises can be considered, as none have been shown to increase blood pressure more than the others when exercise intensity is held constant.[23]

7) Furthermore, focus should be on active exercise to improve strength and joint stability in these patients with generalized joint hypermobility. Accordingly, manual therapy should be used minimally, and joint mobilizations and manipulations should be avoided.

8) Blood pressure and heart rate, as well as symptoms of cardiorespiratory distress and aortic dissection, should be monitored before and immediately after exercise. Consider monitoring these during sustained aerobic exercise.

9) Activity and sport participation decisions should be made ultimately by the patient and family after an adequate education is provided. This education should include the benefits and risks of each activity of interest, current evidence from the literature, and AHA/ACC guidelines and the theory behind them. This will equip the patient and family to make informed decisions, honors their right to be in control of their health choices, and has the potential to reduce participation fears and improve quality of life by avoiding imposing potentially unnecessary restrictions. However, all medical practitioners have the primary responsibility to do no harm. Therefore, it is wise to caution patients from participating in activities and sports that involve high exertion and bodily collision, as these will increase intrathoracic

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pressure and may increase risk of acute aortic dissection. Sports recommended for individuals with TAD by the AHA/ACC include bowling, cricket, curling, golf, riflery, and yoga. Low to moderate intensity hiking, cycling, jogging and swimming are also safe and appropriate activities.

Conclusion

This case report provides an overview of the rare genetic connective tissue disorder, Loeys-Dietz Syndrome, and how a physical rehabilitation expert may optimally evaluate and treat individuals with this condition, despite a lack of high-quality evidence for guidance. To help bridge this knowledge gap, future research should focus on evaluating the longitudinal effect of exercise on aortic dissection risk or survival in patients with thoracic aortic disease in randomized controlled trials. This patient provides an example of the phenotypic variety among patients with LDS, including joint laxity, mitral valve prolapse, scoliosis, pectus excavatum, and a receding chin, in addition to the hallmark sign of aortic root aneurysm. It also demonstrates that that despite these issues, a patient may have minimal to no functional limitations or pain when deciding to seek physical therapy treatment. Accordingly, the aim of rehabilitation was to help the patient achieve their goals of improving general strength to prevent complications, as well as equip the patient how to safely exercise in both the short and long-term by providing education on current evidence mixed with clinical judgement. Low to moderate intensity static and dynamic exercises, activities, and sports, are safe and should be encouraged in patients with LDS for the development and maintenance of a healthy lifestyle.

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