Review of POTS and EDS Pathophysiology, Clinical Presentation & Orthopedic Clinical Considerations

By Rachel LaBella

Introduction:

Physical therapists that have chosen to pursue a career in outpatient orthopedic settings are exposed to a myriad of musculoskeletal conditions. Patients seek physical therapy services for post-operative care, chronic conditions, acute injuries and more, yet therapists often find themselves having to work with, and around, patients' other comorbidities and medical conditions. Medical diagnoses such as Postural Orthostatic Tachycardia Syndrome (POTS) and Ehlers-Danlos Syndrome (EDS) are two such conditions patients may present with that require special considerations by physical therapists. Both conditions affect patient' bodies in a way that alter their cardiovascular and musculoskeletal systems, along with their ability to participate in sports, be physically active, and perform activities of daily living.[1,2,3] It is important for physical therapists to have a better understanding of what these conditions mean with regards to the patients' functional mobility, overall strength, balance, proprioceptive abilities, and activity tolerance. Current evidence even illustrates that there is a connection between POTS and EDS, specifically the hypermobility type, and that those patients diagnosed with both can be challenging to treat effectively.[1]

While both syndromes are not traditionally considered to be commonplace, there are discrepancies within the literature on the exact incidence and prevalence of both POTS and EDS. This is primarily due to the fact both can be challenging to diagnose as POTS falls under the umbrella of dysautonomia, where the autonomic nervous system malfunctions which can result in various other conditions, and EDS has 13 different subtypes created by inherited genetic

variations and mutations.[4,5,6] Data collected in the US currently indicates roughly 0.2 -1.0% of population is diagnosed with POTS, with 80% of those individuals being women where onset occurs between the ages of 15 and 25 years of old. [2,4] Incidence of EDS, and its subtypes, on the other hand is reported to be 1 in 2,500 to 5,000 people with hypermobility subtype (hEDS) being the most common followed by the classical subtype (cEDS). [7,8] With regards to the prevalence of both conditions being present, a recent literary review by Roma et al. noted that in patients with EDS 41% of those individuals had recognized POTS diagnoses and orthostatic symptoms.[1,9] So not only should therapists be cognizant of the pathophysiology, clinical signs and symptoms, diagnostic criteria, and orthopedic considerations of each individual condition, but they should also be prepared to handle individuals who present with both POTS and EDS.

POTS Clinical Presentation & Diagnostic Criteria

As previously indicated POTS stems from cardiovascular autonomic disorder which affects blood flow within the body and is primarily characterized by orthostatic intolerance, excessive heart rate and on occasion syncope or near-syncope. [2,4,10] These key characteristics can be irritated further and increase in severity by changes in internal and external temperature, dehydration, physical strain, emotional stress and infection. [2] While there are different subcategories of POTS, the two main types are neuropathic and hyperadrenergic. [4] Neuropathic POTS is the most commonly diagnosed form of POTS in which sympathetic nerves innervating the lower extremities are defective, preventing blood from being siphoned back to the heart leading to hypotensive blood pressure. [10,11] Hyperadrenergic POTS is the result of excessive amounts of nor-epinephrine circulating and generating increased heart rates and hypertensive blood pressure. [10,11] There are various possible etiologies, some of which are too complex for the

purpose of this paper; however, therapists should be aware that this condition can stem from viral infections, genetic inheritance, inflammatory or autoimmune disorders, or be idiopathic in nature. [2,4] Some notable inflammatory and autoimmune disorders that can be the catalyst for the development of POTS is Sjogrens, Lupus and mixed connective tissue disorders such as EDS which will be expanded upon later in this paper. [2,4] Technically there is no cure for patients diagnosed with POTS however, these individuals have a good prognosis if POTS is managed effectively through pharmacological, dietary, and exercise interventions and lifestyle modifications. [2]

Because of the nature of the condition, POTS patients can present with both cardiovascular related and non-cardiovascular related symptoms. The primary cardiovascular symptoms include "orthostatic intolerance, tachycardia, palpitations, dizziness, lightheadedness, presyncope, and dyspnea." [2,10] Non-cardiovascular characterized symptoms are highly variable and can involve the musculoskeletal, gastrointestinal, respiratory, urogenital and integumentary systems. [2] The non-cardiovascular symptoms patients will primarily present with are generalized deconditioning, exercise intolerance, fatigue, "brain fog," and muscle pain. [2,4] A detailed breakdown of patient symptoms can be found in Appendix 1 Figure 1 from Fedorowski's paper on the clinical presentation and management of POTS. [2] In a separate survey that asked patients what symptoms they have experienced, 95.2% of people experienced fatigue and dizziness, 93.1% experienced brain fog, and 92% experienced heart palpitations. [10] Of these symptoms 71.8% of patients reported fatigue as being "the most challenging symptom" to manage followed by 48.5% reporting dizziness, 43.8% reporting brain fog and 34.9% reporting chronic musculoskeletal pain as being the most challenging. [10]

POTS itself is not necessarily a rare disease, it is just rarely diagnosed by healthcare professionals such as endocrinologists, general practitioners, or cardiologists who most often confirm the diagnoses. [4,10] For patients to be suspected of POTS, they must experience the aforementioned symptoms for at least six months and either exhibit increased heart rate by 30bpm for adults, or 40bpm for adolescents, upon standing or sustained heart rate greater than 120bpm. [2,4,10] Orthostatic hypotension and other conditions that may result in sinus tachycardia such as anxiety, fever, hypothyroidism, anemia or cardioactive drugs cannot be present for an official diagnosis of POTS. [2,4,10] For a detailed breakdown of the diagnostic criteria see Table 1 & 2 in appendix A. Not only must patients fulfill this criterion, but they must also undergo further diagnostic testing including the Tilt Table test, blood labs, echocardiogram, EKG, imaging and occasionally quantitative sudomotor axon reflex testing (QSART). [4,12] The tilt table is the gold standard for testing and requires the patient to lie supine for 20 minutes after which the table is brought to a 70 degree incline where patients remain upright for 40 minutes or until they experience syncope. [2,12,13] A positive test would result in increased heart rate of at least 30 bpm along with POTS related symptoms such as dizziness, syncope, or slight fall in blood pressure. [2,4,12] With regards to a physical therapist's role in diagnosis, it would be pertinent to familiarize oneself with the signs and symptoms associated with the condition so that the therapist may refer the patient to a cardiologist or healthcare provider with access to further diagnostic testing materials.

EDS Clinical Presentation & Diagnostic Criteria

While POTS is the result of autonomic dysfunction, EDS is a connective tissue disorder that is the consequence of a genetic abnormality that affects connective tissue (CT) of the "skin,

muscle, tendons, ligaments, blood vessels, organs, gums, eyes and so on." [3,7] It is primarily "characterized by joint hypermobility, skin hyperextensibility and tissue fragility" which based on current evidence can be categorized into 6 major subtypes but 13 overall classifications (see Table 1 in Appendix B). [8,14,16] Because the tissue is hyperextensible and fragile due to "mutations in collagen synthesis and/or processing", it can exceed functional limitations making strengthening and healing of injured tissue a challenge for physical therapists. [8] The majority of EDS subtypes are inherited autosomal dominant such as Hypermobile EDS (hEDS), which as mentioned before is the most prevalent form, yet some including Classic EDS (cEDS) are autosomal recessive. [6,14] Overall prognoses for individuals with EDS is good, yet evidence exists that those with vascular type EDS may experience a shorter life expectancy due to the prospect of organ and blood vessel ruptures. [7]

Seeing as hEDS is the most prevalent form of EDS, this paper will focus primarily on the symptoms, diagnosis and management of this type and what physical therapists should expect when treating patients with hEDS. The major criteria that define hEDS are hypermobile joints, hyperextensible and velvety skin that can tear or bruise more easily, previous history of dislocations or subluxations and current widespread joint pain. [7,14] Patients with hEDS are also susceptible early onset of osteoarthritis, experience crippling musculoskeletal pain and severe muscle fatigue due to muscle guarding. [7,14,15] Because the clinical presentation is so widespread, adult patients are often misdiagnosed with fibromyalgia and receive ineffective treatments which increases their risk for developing anxiety and depression. [15] Of note, hEDS is also separated into three separate clinical phases the first being "hypermobility phase with marked ligamentous laxity" occurring within the first few months after birth.[14] The second being the pain phase "during the second decade and is characterized by relative decrease in hypermobility and

development of joint muscle and back pain." [14] Lastly, the third phase is the stiffness phase "with progressive limitation of joint motion." [14] Knowing this, the goals of the therapist may change depending on which clinical phase their patient is currently in.

The criteria to officially diagnosis hEDS are extremely complex and a detailed breakdown is included in Appendix B Figures 1& 2 and Table 2&3. [3,6] The first aspect required for a clinical diagnosis is presence of generalized joint hypermobility assessed by the Beighton Score and Five Point Questionnaire. [3,6] A Beighton score of >4 out 9 and pain longer than three months in four separate joints will satisfy this initial requirement. [3,17] The second criteria that must be met is a combination of two or more of what experts classify as Feature A, Feature B, and Feature C which can be found in Appendix B Table 2. [3] Lastly, all of the following criteria in Appendix B Table 3 must be met which includes the exclusion of other CT disorders or autoimmune conditions. [3,6] Because of the extensive criteria required to diagnose hEDS a team of health care professionals must work together with the physical therapist's primary role being the identification of joint hypermobility and assessment of subjective history and pain symptoms.

Connection Between POTS & EDS

Managing either one of these conditions can be a challenge made even more difficult if a patient presents with both POTS and EDS. There are a few proposed mechanisms that hypothesize the connection between POTS and EDS, yet research remains limited and variable. One older hypothesis is that "connective tissue laxity in ligaments and skin also affects vascular wall compliance." [9,18] When this occurs, blood collects more easily in the lower extremity while the individual is upright resulting in increased heart rate and drops in blood pressure. [9,18] Another possible mechanism is "peripheral neuropathy affecting sympathetic fibers in joint hypermobility

and EDS patients" [9,19] A trial by Gazit et al. studied 48 individuals diagnosed with EDS who were also experiencing orthostatic symptoms. [18] All participants reported experiencing these symptoms for longer than 6 months, which as previously mentioned is one of the diagnostic criteria for POTS. [2,19] It was also found that a greater percentage of these individuals had a lower standing tolerance and experienced postural tachycardia, lightheadedness, and impaired concentration than did the control group of health individuals. [19] Furthermore, Wandele et al. continued to assess the connection between EDS, specifically hEDS, and autonomic dysfunction in three separate comprehensive studies. [20,21,22] In the 2014 studies, Wandele et al. found that hEDS patients "had the highest autonomic symptom burden" and 94% of those patients experienced orthostatic intolerance and associated symptoms. [20,21] In the follow up study Wandele et al. focused more on the fatigue aspect of patients undergoing the tilt table test for POTS. [22] They found that for those individuals who were already diagnosed with hEDS, the severity of fatigue, assessed on a scale of 0 to 10 (with 10 being extremely fatigued/exhausted), increased significantly more than the control group. [22] Whether the connection between POTS and EDS are the result of any of the previously mentioned mechanisms, these two studies clearly demonstrate a connection between the two conditions. This in turn supports Roma et al.'s research mentioned earlier where 41% of individuals with EDS were found to be positive for POTS. [9]

Initial Evaluation & Patient Presentation

So, what does all of this mean in terms of a physical therapists' evaluation and management of patients with POTS, EDS or both? For patients with suspected or diagnosed POTS or EDS, upon initial examination it's imperative to take a detailed subjective history.

Patients suspect for hEDS may report general pain and fatigue, history of subluxations or dislocations along with past experiences in gymnastics or ballet, which require excessive amounts of flexibility, bruising easily, or being uncomfortable when sustaining sitting or standing for long periods of time. [4,23] As for POTS, a typical POTS patient may present as female between the ages of 15-25 and report symptoms such as dizziness, syncope, fatigue, exercise intolerance, brain fog and an increase in symptoms upon transitions from supine to sitting or standing. [2,4] At this point the subjective history should prompt therapists to suspect the possibility of POTS or EDS and begin to conduct more objective assessments.

In the clinic the therapist can have the patient perform the Beighton scale to assess presence of joint hypermobility and check heart rate and blood pressure upon transition from supine to standing to gauge presence of orthostatic intolerance. Children and adults with EDS may also present with reduce proprioceptive abilities and balance deficits. [23] Because of the increased extensibility of the tissue, mechanoreceptors housed in ligaments, tendons and capsules do not receive the same mechanical stimulation which affect the body's ability to detect joint position. To assess this, the presiding therapist may have the patient perform a Rhomberg test or the balance subsection of Bruininks-Ostersky for children. [23]

Decreased muscle strength, muscle fatigue and exercise intolerance are associated with both EDS and POTS and should also be tested upon initial evaluation. For patients with EDS, strength deficits may be the result of an ineffective length-tension relationship therefore resulting in global muscular dysfunction, gait abnormalities, activity limitations, and increased incidence of subluxations or dislocations. Muscular fatigue in EDS patients appears to be primarily due to their reliance on their muscles to protect their joints as the laxity in ligaments and capsules do not provide joint stability. [14,24] With respect to patients with POTS, there is limited research on

the exact pathophysiology behind why they experience muscular weakness and fatigue. The primary hypothesis attributes the above-mentioned factors to the relatively smaller heart size found in these patients. [4,25,26] The smaller heart results in decreased stroke volume which in turn reduces cardiac output. [4,25,26] Decreased cardiac output means less oxygenated blood is being pumped to working muscles preventing them from working efficiently. [4,25,26] Heart size is also responsible for patients' exercise intolerance as POTS patients "have excessive increase in heart rate and reduced stroke volume for each level of absolute workload" which contributes to lower peak VO2 volume and cardiovascular fitness. [26] So these patients are unable to pump enough oxygenated blood to working muscles which results in fatigue and weakness and therefore can affect their abilities to engaged in exercise and activities of daily living if not properly managed.

Interventions & Orthopedic Considerations

To address these deficits in strength, exercise intolerance, proprioception, balance and joint stability while maintaining awareness of positional intolerance, physical therapists have to get creative with their intervention programs for patients with POTS and EDS. Current evidence supports the need for mild to moderate progressive strength and endurance training where POTS patients begin in a recumbent or semi-recumbent position so as not to elicit orthostatic symptoms. [2,26] Patients may be wary of engaging in a new exercise program as it can cause an increase in symptom severity however, it would be incumbent upon therapists to explain that physical deconditioning only adds to the problem. For example, patients who were sedentary or under chronic bed rest exhibited ventricular remodeling which further decreased stroke volume "ultimately resulting in reflex tachycardia" and further exercise intolerance. [26] On the other hand,

patients who engaged in short term exercise training showed increases in "cardiac size and mass, blood volume and VO2 peak" as well as increased orthostatic tolerance. [26]

Whether treating POTS in isolation or treating a different pathology in a patient who has POTS, interventions should include strength, endurance and postural training. [26,27] Therapists should use a recumbent bicycle initially with these patients then progress to more upright exercises for longer periods of time to address cardiorespiratory deficits while being cognizant of positional intolerance. [4,26,27] Resistance training should also be completed in supine or semi-recumbent positions initially with progressive upper and lower extremity and core strengthening exercises. [4,26,27] Because some patients with POTS may experience more severe symptoms of orthostatic intolerance in upright positions, postural training is a necessary aspect to include in the treatment program. A simple initial exercise to include would be static standing with 30 second progressions until 10 minutes is reached without symptom exacerbation. [4,26] The Levine protocol referenced above, and in Appendix C Figure 1, was designed specifically for treating patients with POTS, but the principles and postural considerations included can be adapted to fit an outpatient orthopedic population. [26,27]

While the primary concern when working with POTS patients is their positional and exercise intolerance, therapists need to be aware of muscles that promote instability and extremes of range of motion in EDS patients. There is not a lot of data on specific protocols when working with hEDS patients, yet the research is similar to POTS in that it recommends progressive endurance, strength and postural training. [14,23,24] Physical therapists should focus on strengthening larger muscle groups that promote stability and dynamic control to reduce muscle fatigue and risk of dislocation or subluxation. [14,23,24] For example, in hEDS patients with recurrent anterior glenohumeral joint instability, strengthening muscles that impose excessive

anteriorly directed forces would only increase the risk of anterior dislocation or subluxation. Additionally, positions of so called "arthrokinematic danger" and extremes of range of motion during resistance training should be avoided so as to reduce tensile strain on capsular and ligamentous tissues. [14,23,24] When hEDS patients are placed in extreme positions those already lengthened tissues lengthen even more resulting in greater hypermobility and instability. [14,23,24] Strengthening can only help patients so much however, and some may require bracing or external supports to correct malalignments and improve stability. This benefits the patient in that they now rely less on their muscles to provide constant stability which can decrease overall muscle fatigue and pain.[14,23,24]

In addition to the above orthopedic interventions, patients with hEDS who present with gait abnormalities and balance or proprioceptive deficits require further intervention. Oftentimes it is the "combination of hypermobile joints, reduced proprioception, altered motor control, weak muscles and reduced stamina" that cause gait deviations and balance inadequacy. [28] Therefore, physical therapists are encouraged to use visual feedback via mirrors or self-recordings so their patients may increase awareness of their postural and gait irregularities in addition to strength training. [28,29] Previously mentioned was the use of braces or external supports to reduce muscular fatigue yet these can also be used to help improve gait. For example, hEDS patients can exhibit excessive pronation as a result of hypermobility that then causes further injury to the lower extremity. [28] The use of a medial wedge and a supportive shoe can help to reduce pronation, consequently reducing further damage to the lower extremity during ambulation or weightbearing activities. To improve hEDS patients' balance and proprioceptive abilities, in addition to improving overall awareness of their body mechanics through visual feedback,

exercises using balance boards, unstable surfaces and rhythmic stabilizations have been shown to improve stability and position sense. [24,28,29]

Other considerations when it comes to a physical therapist's role in treating patients with POTS and EDS is patient education and lifestyle modification to improve overall quality of life. Managing both conditions generally requires a team of healthcare professionals, yet physical therapists should be comfortable informing patients on the basics of the pathophysiology behind their condition, how it affects their daily life, the benefits of exercise, and dietary and behavioral changes that can be made to reduce severity of symptoms. For patients with POTS especially, diet, water intake, and sleep habits are important to review. These patients should try and limit caffeine as much as possible, take in 2-4 liters of water per day, and avoid sleeping greater than 12 hours a day. [2,4,27] The most important thing a physical therapist can do however is facilitate regular exercise habits in patients with POTS and EDS. Patients will often avoid being physically active due to pain, weakness, positional intolerance and fatigue choosing instead to live a sedentary lifestyle which only exacerbates musculoskeletal and cardiovascular complications. By educating the patient on the benefits of exercise and adapting exercise programs or physical activities so they fit better into the patient's daily life, physical therapists can improve overall adherence.

Conclusion

In conclusion the evaluation, management and treatment of patients with Postural Orthostatic Tachycardia Syndrome and Ehlers-Danlos Syndrome is complex. POTS is a form of dysautonomia that is characterized by increased heart rate and orthostatic intolerance with symptoms including dizziness, exercise intolerance, and a global muscular weakness. [2]

Interventions in those with POTS should therefore focus on progressive resistance, endurance and postural training beginning with a low frequency, magnitude and duration of exercises in recumbent or semi-recumbent positions as highlighted in the Levine Protocol.[2,27] EDS, specifical hypermobility type EDS, is an autosomal dominant connective tissue disorder that is characterized by joint hypermobility and skin hyperextensibility with symptoms including widespread pain, muscle fatigue and weakness, risk for joint dislocation, balance deficits and gait abnormalities.[7,14] Effective interventions for patients are similar to those with POTS with the addition of gait training, balance exercises and bracing or orthotics if necessary.[28] Whether treating EDS, POTS, or treating a musculoskeletal injury in a patient who has either condition, physical therapists must be conscious of the effects each syndrome has on the body to provide the most effective treatment.

Appendix A -POTS

Figure 1: Fedorowski Symptom Table

Cardiovascular symptoms *(pathognomonic)*	
Cardiovascular system	Main: *Orthostatic intolerance, orthostatic tachycardia, palpitations, dizziness, lightheadedness, presyncope, exercise intolerance*
	Other frequent symptoms: dyspnoea, chest pain/discomfort, acrocyanosis, Raynaud's phenomenon, venous pooling, limb oedema
Noncardiovascular symptoms (accompanying)	
General symptoms	General deconditioning, chronic fatigue, exhaustion, heat intolerance, fever, debility, bedriddenness
Nervous system	Headache/migraine, mental clouding ('brain fog'), cognitive impairment, concentration problems, anxiety, tremulousness, light and sound sensitivity, blurred/tunnel vision, neuropathic pain (regional), sleeping disorders, involuntary movements
Musculoskeletal system	Muscle fatigue, weakness, muscle pain
Gastrointestinal system	Nausea, dysmotility, gastroparesis, constipation, diarrhoea, abdominal pain, weight loss
Respiratory system	Hyperventilation, bronchial asthma, shortness of breath
Urogenital system	Bladder dysfunction, nycturia, polyuria
Skin	Petechiae, rashes, erythema, telangiectasias, abnormal sudomotor regulation, diaphoresis, pallor, flushing

Fedorowski et al. aimed to review the overall clinical presentation of POTS and provided a detailed description of patient management in addition to steps healthcare providers should take.[2] *Above is the breakdown of cardiovascular and non-cardiovascular symptoms seen in patients with either neuropathic or hyperadrenergic POTS.*

Table 1. Diagnostic criteria for POTS

Must Have:	History of POTS related symptoms (seen in Figure 1) for *at least* 6 months - *Ex. orthostatic intolerance, dizziness, tachycardia, brain fog etc*.
Including: [2,4,10]	**Increased heart rate within 10** minutes of standing (or tilt table test) by: ≥ 30bpm for adults (≥40bpm for adolescents) ~OR~ ≥ 120 bpm for adults **Lack presence** of orthostatic hypotension (drop in BP of 20mmHG systolic or 10mmHg diastolic) within 5 minutes of standing. **Reproduction or exacerbation** of symptoms (see Figure 1) upon standing and reduced when recumbent. **Absence of** "conditions provoking sinus tachycardia such as anxiety disorders, hyperventilation, anemia, fever, pain, infection, dehydration, hyperthyroidism, pheochromocytoma, use of cardioactive drugs (sympathomimetics, anticholinergics" [2]
Diagnostic Testing [2,12]	• Standing Test • Tilt Table Test* • EKG • Echocardiogram • Blood Tests • Quantitative Sudomotor Axon Reflex Testing (QSART) • CT/MRI

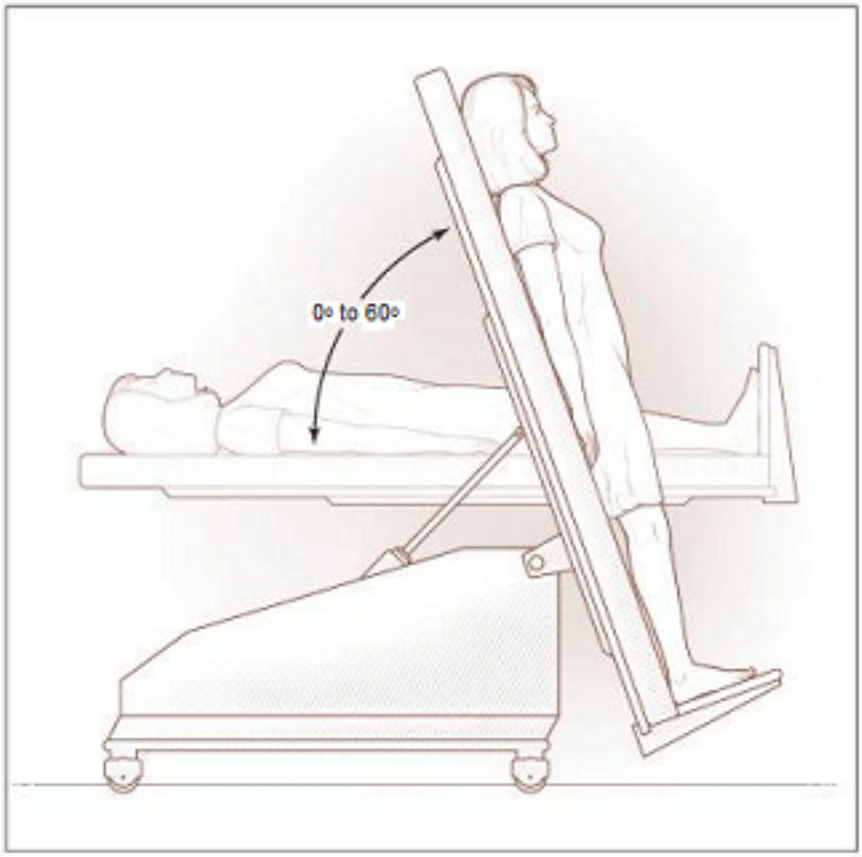
Individuals must present with the following criteria to receive a diagnosis of POTS. The gold standard for diagnostic tests is the Tilt Table Test, but often patients with undergo further testing to rule out other potential diagnoses.*[2,12]*Blood labs are taken to assess the possibility of other conditions hypothyroidism and lupus and vitamin deficiencies such as B12 and vitamin D.* [12] *Listed below in Table 2 is a more detailed explanation of diagnostic testing that patients undergo.* [2]

Table 2. Fedorowski Diagnostic Testing/Modalities Table

Diagnostic test	Diagnostic outcome	Comment
Head-up tilt test with non-invasive beat-to-beat monitoring (Fig. 2)	The characteristic orthostatic sinus tachycardia and reproduction of symptoms. The absence of orthostatic hypotension (Table 1)	'The golden standard' in POTS diagnostic 1, 4, 62, 63
24 (48)-h ECG monitoring (Fig. 3)	Heart rate accelerations during daytime and in the morning after awakening. Normal heart rate night-time. Reduced heart rate variability	The test may be used to confirm the diagnosis and to discriminate POTS from inappropriate sinus tachycardia (elevated heart rate >90 bpm during 24 h and the absence of typical night-time dip) 3, 4
External or implantable loop recorders (ILRs)	ECG record of spontaneous fainting spells. Brady- or tachyarrhythmia. Epilepsy. Psychogenic pseudosyncope Heart rate control	In very difficult diagnostic cases with multiple syncopal events, traumatic syncope, amnesia, therapy resistance, clinical suspicion of arrhythmia and epilepsy, this method might be recommended under restriction. Principally, it should be reserved for experts with good insights into the POTS and syncope pathophysiology. When implanted for other reasons, ILR might be used for heart rate monitoring during therapy

Diagnostic test	Diagnostic outcome	Comment
24-h ambulatory BP monitoring	Hypertensive or hypotensive tendency. Low-BP phenotype	The results of BP monitoring may be used for tailoring the therapy with cardiovascular drugs. The hypovolaemic type of POTS usually demonstrates hypotensive tendency and low-BP phenotype may be targeted by vasoactive and volume-expanding drugs 4
Exercise ECG	The grade of overall physical performance compromise and abnormal haemodynamic responses during exercise	This method may be used for quantification of remaining physical capacity and may play role in tailoring the physical therapy. It may also be recommended if patient faints during exercise
Echocardiography	Structural cardiac changes	Echocardiography is recommended for exclusion of possible underlying cardiac changes if physical findings and basic cardiac workup suggests the presence of structural changes in the heart.
Valsalva manoeuvre	Exaggerated BP and heart rate overshoot in phase IV	It may be used as a confirmatory test; it also suggests the presence of 'hyperadrenergic' type of POTS 34, 62
Active standing test	The same diagnostic criteria as for head-up tilt test (Table 1)	It may be used for initial screening and in clinics that lack access to fully equipped autonomic laboratory 5. The chronotropic response may be blunted by patient using muscle pump 4, 5, 74

Figure 2: Tilt Table Test Figure [13]



When conducting the tilt table test, the patient would be hooked up to a heart rate and BP monitor and potentially an IV to monitor vitals. In the figure above, the table is elevated to 60 degrees, but testing can occur anywhere between 60-80 degrees. [12,13]

Appendix B - EDS

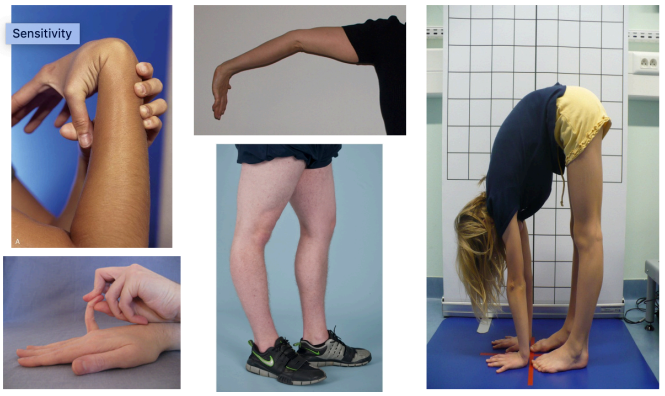
Table 1. Classification and Genetic causes of EDS (14,16)

Type	Major Criteria	Minor Criteria	Inheritance	Genetic Defect
Classical	Skin hyperextensibility, widened atrophic scars, joint hypermobility	Smooth skin, molluscoid pseudotumors, subcutaneous spheroids, joint hypermobility, easy bruising, tissue fragility, positive family history	Autosomal dominant	Abnormal type V collagen (*COL5A1* and *COL5A2* genes)
Hypermobility	Skin involvement, generalized joint hypermobility	Recurrent joint dislocations, chronic limb pain, positive family history	Autosomal dominant[a]	Reduction in tenascin X (responsible for a small percentage of hypermobility cases)
Vascular	Thin skin; arterial, intestinal, or uterine fragility; extensive bruising; characteristic facial appearance	Acrogeria, small joint hypermobility, tendon or muscle rupture, clubfoot, early onset varicose veins, arteriovenous fistulae, pneumothorax, gingival recession, positive family history	Autosomal dominant	Structural defects of type III collagen (*COL3A1* gene)
Kyphoscoliosis	Generalized joint laxity, severe muscle hypotonia, scoliosis, scleral fragility	Tissue fragility, easy bruising, arterial rupture, Marfanoid habitus, microcornea, osteopenia, positive family history	Autosomal recessive	Deficiency of lysyl hydroxylase (collagen modifying enzyme)
Arthrochalasia	Severe joint hypermobility with subluxations and congenital hip dislocations	Skin hyperextensibility, tissue fragility, easy bruising, muscle hypotonia, kyphoscoliosis, osteopenia	Autosomal dominant	Deficiency of chains in type I collagen (skipped exon 6 in *COL1A1* or *COL1A2* genes)
Dermatosparaxis	Skin fragility, redundant skin	Soft skin, easy bruising, premature rupture of fetal membranes, umbilical or inguinal hernias	Autosomal recessive	Deficiency of procollagen I (*ADAMST2* gene)

Above are the 6 traditional categories of EDS, although current classification systems have now included a total of 13 variations of EDS. Hypermobility type and Classical type are still the two most commonly seen based off recent evidence. [14,16]

Figure 1. Beighton Scale [14,17]

CLINICAL MANEUVER	UNABLE TO PERFORM (0 POINTS)	ABLE TO PERFORM (1 POINT)
Apposition of thumb to forearm		
Right	0	1
Left	0	1
Extension of fifth finger beyond 90 degrees		
Right	0	1
Left	0	1
Extension of elbow beyond 10 degrees		
Right	0	1
Left	0	1
Extension of knee beyond 10 degrees		
Right	0	1
Left	0	1
Forward flexion of trunk, legs straight, palms touching floor	0	1
Total Beighton Score (sum of points for each maneuver)	0 to 9 points	



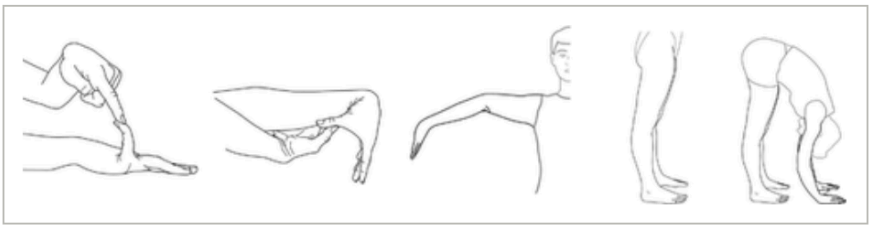
The Beighton Score is the primary measure to assess joint hypermobility in patients suspected of hEDS. However, it is important to keep in mind that children and adolescents are generally more mobile than adults leading to potential overdiagnosis in younger individuals than adults especially as adults' transition to the third clinical phase characterized by stiffness. [3,14,17]

Figure 2. Five Point Questionnaire

Table III. The Five-Point Questionnaire. Adapted From [Grahame and Hakim, 2003]

1. Can you now (or could you ever) place your hands flat on the floor without bending your knees?
2. Can you now (or could you ever) bend your thumb to touch your forearm?
3. As a child, did you amuse your friends by contorting your body into strange shapes or could you do the splits?
4. As a child or teenager, did your shoulder or kneecap dislocate on more than one occasion?
5. Do you consider yourself "double-jointed"?

A "yes" answer to two or more questions suggests joint hypermobility with 80–85% sensitivity and 80–90% specificity



The Five Point questionnaire above is used primarily for patients that score lower on the Beighton scale in joints such as the TMK, shoulder, hip, foot, wrist, ankle and digits. [3] *However, the Beighton Score is still the primary assessment for joint hypermobility.*

Table 2. Second Criteria for Diagnosing hEDS

Feature A [3]	Systemic manifestations of a more generalized CT disorder, 5 must be present	• unusually soft or velvety skin • mild skin hyperextensibility • unexplained striae at back, groins, thighs, breasts, abdomen, w/out signification hx of gain or loss of body fat or weight • bilateral piezogenic papules of heel • recurrent or multiple abdominal hernias • atrophic scarring involving at least two sites and without the formation of truly papyraceous and/or hemosiderin scars • pelvic floor, rectal. And/or uterine prolapse • dental crowding and high or narrow palate • arachnodactyly as defined in one or more of the following (1) positive wrist sign on both sides (Steinberg) (2) positive thumb sign (walker sign) on both sides • arm span to height > 1.05 • mitral valve prolapse • aortic root dilation
Feature B [3]	Positive family history, with one or more first degree relatives independently meeting the current diagnostic criteria for hEDS	
Feature C [3]	Musculoskeletal complications	• musculoskeletal pain in two or more limbs, recurring daily for at least 3 months • chronic widespread pain for > 3 months • recurrent joint dislocations or frank joint instability in absence of trauma (a) three or more atraumatic dislocations in the same joint or two or more atraumatic dislocations in two different joints occurring at different times (b) medical confirmation of joint instability at two or more sites not related to trauma

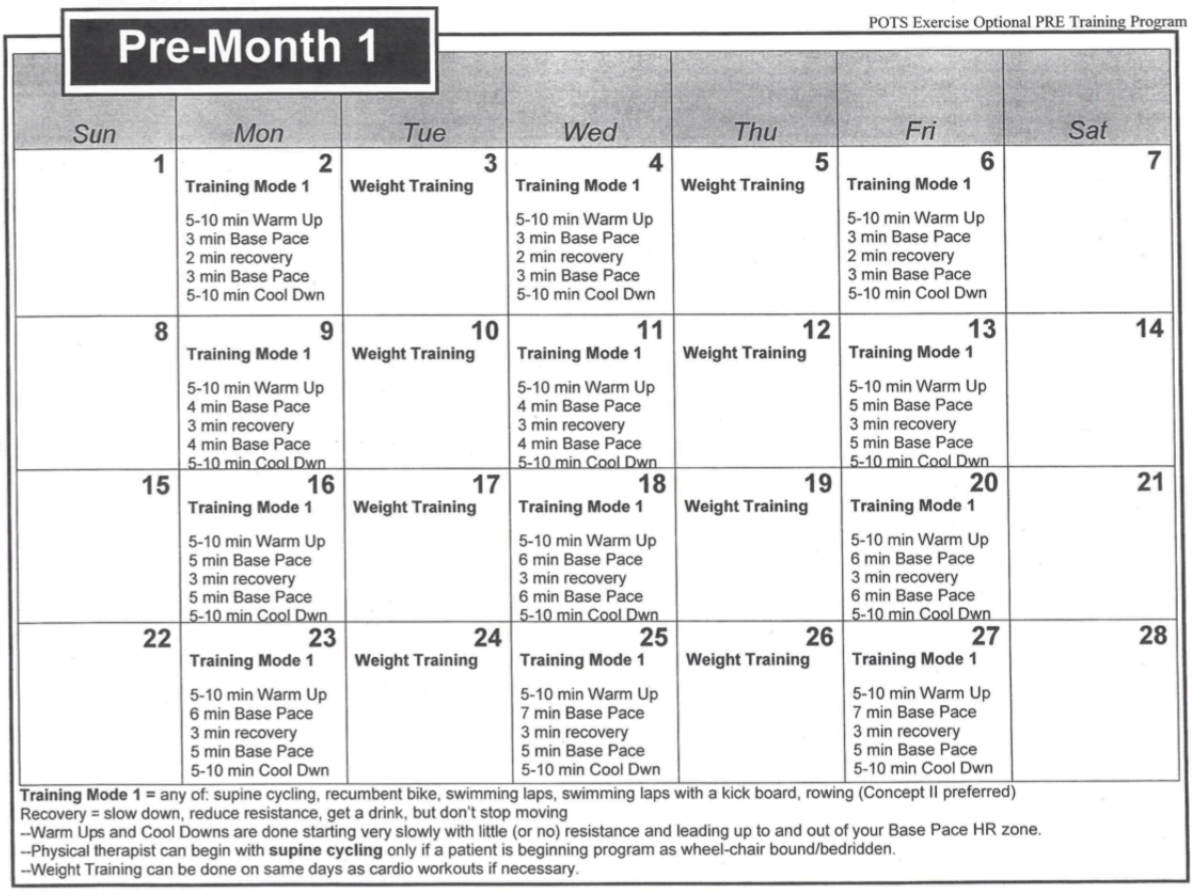
To meet the second criteria for hEDS the patient must present with "two or more of the following features (A&B, A&C, B&C, or A & B & C)." [3,6]

Table 3. Third Criteria for Diagnosing hEDS [3,6]

The following must be met:	• "Absence of unusual skin fragility which should prompt consideration of other types of EDS • Exclusion of other heritable and acquired CT disorders including autoimmune rheumatologic conditions • Exclusion of alternative diagnoses that may also include joint hypermobility by means of hypotonia and/or CT laxity" [3,6]

Appendix C – Clinical Consideration's/Interventions

Figure 1. Sample Levine POTS Therapy Program [26,27]



POTS Exercise Optional PRE Training Program

Pre-Month 1

Sun	Mon	Tue	Wed	Thu	Fri	Sat
1	2 **Training Mode 1** 5-10 min Warm Up 3 min Base Pace 2 min recovery 3 min Base Pace 5-10 min Cool Dwn	3 **Weight Training**	4 **Training Mode 1** 5-10 min Warm Up 3 min Base Pace 2 min recovery 3 min Base Pace 5-10 min Cool Dwn	5 **Weight Training**	6 **Training Mode 1** 5-10 min Warm Up 3 min Base Pace 2 min recovery 3 min Base Pace 5-10 min Cool Dwn	7
8	9 **Training Mode 1** 5-10 min Warm Up 4 min Base Pace 3 min recovery 4 min Base Pace 5-10 min Cool Dwn	10 **Weight Training**	11 **Training Mode 1** 5-10 min Warm Up 4 min Base Pace 3 min recovery 4 min Base Pace 5-10 min Cool Dwn	12 **Weight Training**	13 **Training Mode 1** 5-10 min Warm Up 5 min Base Pace 3 min recovery 5 min Base Pace 5-10 min Cool Dwn	14
15	16 **Training Mode 1** 5-10 min Warm Up 5 min Base Pace 3 min recovery 5 min Base Pace 5-10 min Cool Dwn	17 **Weight Training**	18 **Training Mode 1** 5-10 min Warm Up 6 min Base Pace 3 min recovery 6 min Base Pace 5-10 min Cool Dwn	19 **Weight Training**	20 **Training Mode 1** 5-10 min Warm Up 6 min Base Pace 3 min recovery 6 min Base Pace 5-10 min Cool Dwn	21
22	23 **Training Mode 1** 5-10 min Warm Up 6 min Base Pace 3 min recovery 5 min Base Pace 5-10 min Cool Dwn	24 **Weight Training**	25 **Training Mode 1** 5-10 min Warm Up 7 min Base Pace 3 min recovery 5 min Base Pace 5-10 min Cool Dwn	26 **Weight Training**	27 **Training Mode 1** 5-10 min Warm Up 7 min Base Pace 3 min recovery 5 min Base Pace 5-10 min Cool Dwn	28

Training Mode 1 = any of: supine cycling, recumbent bike, swimming laps, swimming laps with a kick board, rowing (Concept II preferred)
Recovery = slow down, reduce resistance, get a drink, but don't stop moving
--Warm Ups and Cool Downs are done starting very slowly with little (or no) resistance and leading up to and out of your Base Pace HR zone.
--Physical therapist can begin with **supine cycling** only if a patient is beginning program as wheel-chair bound/bedridden.
--Weight Training can be done on same days as cardio workouts if necessary.

Pre-Month 2

Sun	Mon	Tue	Wed	Thu	Fri	Sat
1	2 **Training Mode 1** 10 min Warm Up 5 min Base Pace 2 min recovery 5 min Base Pace 2 min recovery 5 min Base Pace 10 min Cool Down	3 **Weight Training**	4 **Training Mode 1** 10 min Warm Up 5 min Base Pace 2 min recovery 5 min Base Pace 2 min recovery 5 min Base Pace 10 min Cool Down	5 **Weight Training**	6 **Training Mode 1** 10 min Warm Up 5 min Base Pace 2 min recovery 5 min Base Pace 2 min recovery 5 min Base Pace 10 min Cool Down	7
8	9 **Training Mode 1** 10 min Warm Up 6 min Base Pace 2 min recovery 6 min Base Pace 2 min recovery 6 min Base Pace 10 min Cool Down	10 **Weight Training**	11 **Training Mode 1** 10 min Warm Up 7 min Base Pace 2 min recovery 7 min Base Pace 2 min recovery 7 min Base Pace 10 min Cool Down	12 **Weight Training**	13 **Training Mode 1** 10 min Warm Up 8 min Base Pace 2 min recovery 8 min Base Pace 2 min recovery 8 min Base Pace 10 min Cool Down	14
15	16 **Training Mode 1** 10 min Warm Up 10 min Base Pace 3 min recovery 10 min Base Pace 10 min Cool Down	17 **Weight Training**	18 **Training Mode 1** 10 min Warm Up 11 min Base Pace 3 min recovery 11 min Base Pace 10 min Cool Down	19 **Weight Training**	20 **Training Mode 1** 10 min Warm Up 12 min Base Pace 3 min recovery 12 min Base Pace 10 min Cool Down	21
22	23 **Training Mode 1** 10 min Warm Up 13 min Base Pace 4 min recovery 13 min Base Pace 10 min Cool Down	24 **Weight Training**	25 **Training Mode 1** 10 min Warm Up 14 min Base Pace 5 min recovery 14 min Base Pace 10 min Cool Down	26 **Weight Training**	27 **Training Mode 1** 10 min Warm Up 15 min Base Pace 5 min recovery 15 min Base Pace 10 min Cool Down	28
29	30 **Training Mode 1** 10 min Warm Up 20 min Base Pace 10 min Cool Down	31 **Weight Training**	32 **Training Mode 1** 10 min Warm Up 24 min Base Pace 10 min Cool Down	33 **Weight Training**	34 **Training Mode 1** 10 min Warm Up 27 min Base Pace 10 min Cool Down	35

Training Mode 1 = any of: supine cycling, recumbent bike, swimming laps, swimming laps with a kick board, rowing (Concept II preferred)
Recovery = slow down, reduce resistance, get a drink, but don't stop moving
--Warm Ups and Cool Downs are done very slowly with little resistance and leading up to and out of your Base Pace HR zone.
--Weight Training can be done on same days as cardio workouts if necessary

Month 1

Sun	Mon	Tue	Wed	Thu	Fri	Sat
1	2 **Training Mode 1** 5 min Warm-Up 30 min Base Pace 5 min Cool-down	3 **Weight Training**	4 **Training Mode 1** 5 min Warm-Up 30 min Base Pace 5 min Cool-down	5 **Weight Training**	6 **Training Mode 1** 5 min Warm-Up 30 min Base Pace 5 min Cool-down	7
8	9 **Training Mode 1** 5 min Warm-Up 30 min Base Pace 5 min Cool-down	5 **Weight Training**	11 **Training Mode 1** 5 min Warm-Up 30 min Base Pace 5 min Cool-down	12 **Weight Training**	13 **Training Mode 1** 5 min Warm-Up 20 min **MSS** 5 min Cool-down	14 **Training Mode 1** 40 min Recovery
15	16 **Training Mode 1** 5 min Warm-Up 30 min Base Pace 5 min Cool-down	17 **Weight Training**	18 **Training Mode 1** 5 min Warm-Up 30 min Base Pace 5 min Cool-down	19 **Weight Training**	20 **Training Mode 1** 5 min Warm-Up 30 min Base Pace 5 min Cool-down	21
22	23 **Training Mode 1** 5 min Warm-Up 30 min Base Pace 5 min Cool-down	24 **Weight Training**	25 **Training Mode 1** 5 min Warm-Up 25 min **MSS** 5 min Cool-down	26 **Training Mode 1** 40 min Recovery	27 **Weight Training**	28 **Training Mode 1** 5 min Warm-Up 30 min Base Pace 5 min Cool-down

Training Mode 1 = Any of: Recumbent Biking, Swimming, Rowing (Concept II preferred)
Weight Training can be done on same days as Cardio workouts if necessary.

Month 2

Sun	Mon	Tue	Wed	Thu	Fri	Sat
1	2 **Training Mode 1** 5 min Warm-Up 30 min Base Pace 5 min Cool-down	3 **Weight Training**	4 **Training Mode 2** 5 min Warm-Up 20 min Base Pace 5 min Cool-down	5 **Weight Training**	6 **Training Mode 2** 5 min Warm-Up 20 min Base Pace 5 min Cool-down	7
8 **Training Mode 1-2** 5 min Warm-Up 30 min Base Pace 5 min Cool-down	9 **Weight Training**	5 **Training Mode 2** 5 min Warm-Up 30 min Base Pace 5 min Cool-down	11 **Weight Training**	12 **Training Mode 1-2** 5 min Warm-Up 25 min **MSS** 5 min Cool-down	13 **Training Mode 1** 40 min Recovery	14
15 **Training Mode 1-2** 5 min Warm-Up 40 min Base Pace 5 min Cool-down	16 **Weight Training**	17	18 **Training Mode 1-2** 5 min Warm-Up 30 min **MSS** 5 min Cool-down	19 **Training Mode 1** 40 min Recovery	20 **Weight Training**	21 **Training Mode 1-2** 5 min Warm-Up 35 min Base Pace 5 min Cool-down
22	23 **Weight Training**	24 **Training Mode 1-2** 5 min Warm-Up 35 min **MSS** 5 min Cool-down	25 **Training Mode 1** 40 min Recovery	26 **Training Mode 2-3** 5 min Warm-Up 30 min Base Pace 5 min Cool-down	27 **Weight Training**	28 **Training Mode 1-2** 5 min Warm-Up 40 min Base Pace 5 min Cool-down

Training Mode 1 = Any of: Recumbent Biking, Swimming, Rowing (Concept II preferred)
Training Mode 1-2 = Either Upright bike or Rowing
Training Mode 2 = Upright Bike
Training Mode 2-3 = Any of: Upright Bike, Treadmill walking (flat grade), Elliptical (stationary arms)
Weight Training can be done on same days as Cardio workouts if necessary.

Month 3

Sun	Mon	Tue	Wed	Thu	Fri	Sat
1	2 **Training Mode 2-3** 5 min Warm-Up 35 min Base Pace 5 min Cool-down	3 **Weight Training**	4 **Training Mode 2-3** 5 min Warm-Up 35 min Base Pace 5 min Cool-down	5 **Weight Training**	6 **Training Mode 2-3** 5 min Warm-Up 35 min Base Pace 5 min Cool-down	7
8	9 **Training Mode 2-3** 5 min Warm-Up 40 min Base Pace 5 min Cool-down	5 **Weight Training**	11 **Training Mode 3** 5 min Warm-Up 30 min **MSS** 5 min Cool-down	12 **Training Mode 2-3** 40 min Recovery **Weight Training**	13 **Training Mode 2-3** 5 min Warm-Up 35 min Base Pace 5 min Cool-down	14
15	16 **Training Mode 2-3** 5 min Warm-Up 60 min Base Pace 5 min Cool-down	17 **Weight Training**	18 **Training Mode 2-3** 5 min Warm-Up 30 min Base Pace 5 min Cool-down	19 **Training Mode 3** 5 min Warm-Up 35 min **MSS** 5 min Cool-down	20 **Training Mode 2-3** 25 min Recovery **Weight Training**	21 **Training Mode 2-3** 5 min Warm-Up 50 min Base Pace 5 min Cool-down
22	23 **Training Mode 3** 5 min Warm-Up 35 min Base Pace 5 min Cool-down	24 **Weight Training**	25 **Training Mode 2-3** 5 min Warm-Up 45 min Base Pace 5 min Cool-down	26 **Training Mode 3** 5 min Warm-Up 40 min **MSS** 5 min Cool-down	27 **Training Mode 2-3** 25 min Recovery **Weight Training**	28

Training Mode 2-3 = Any of: Rowing, Upright Bike, Treadmill Walking, Elliptical – MIX IT UP when ready to the more upright modes!
Training Mode 3 = If you're ready: Treadmill Walking or Elliptical. (If not stick with Rowing and Upright Bike.)
Weight Training can be done on same days as Cardio workouts if necessary.

Month 4

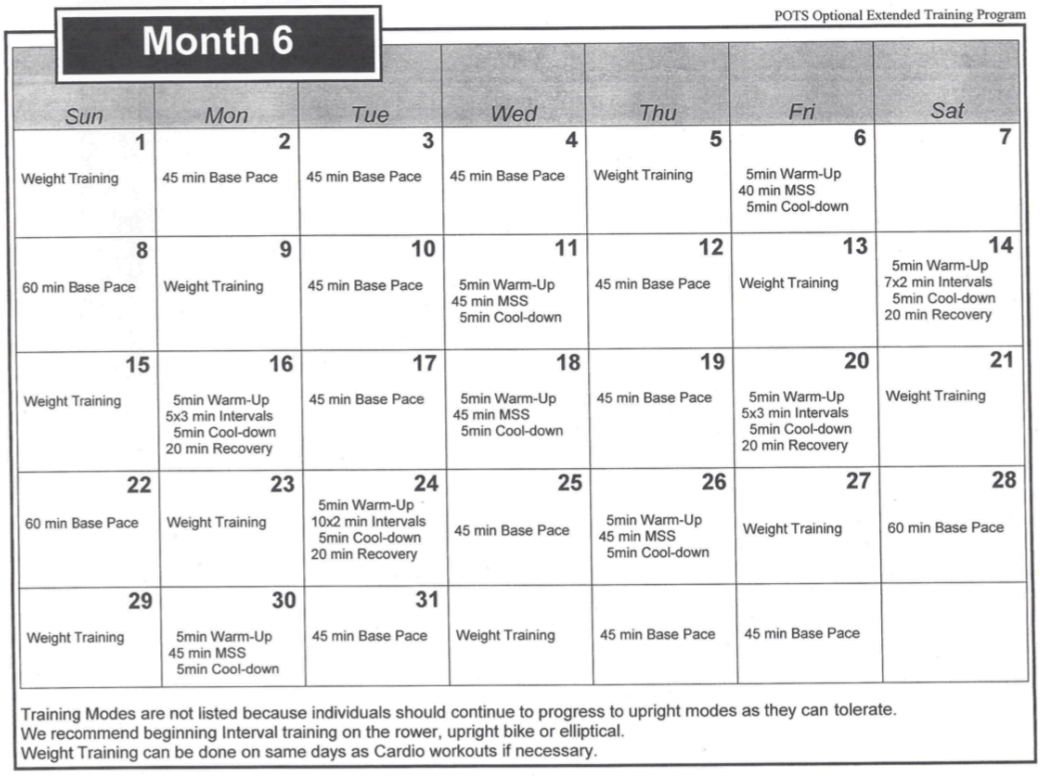
Sun	Mon	Tue	Wed	Thu	Fri	Sat
1 45 min Base Pace	2 Weight Training	3 40 min Base Pace	4 60 min Base Pace	5 Weight Training	6 45 min Base Pace	7
8 Weight Training	9 30 min Base Pace	5 5 min Warm-Up 3x1 min Intervals 5 min Cool-down 20 min Recovery	11 45 min Base Pace	12 Weight Training	13 5 min Warm-Up 30 min MSS 5 min Cool-down	14
15 Weight Training	16 35 min Base Pace	17 5 min Warm-Up 35 min MSS 5 min Cool-down	18 Weight Training	19 5 min Warm-Up 4x1 min Intervals 5 min Cool-down 20 min Recovery	20 40 min Base Pace	21 25 min Recovery
22 60 min Base Pace	23 Weight Training	24 5 min Warm-Up 5x1 min Intervals 5 min Cool-down 20 min Recovery	25 45 min Base Pace	26 Weight Training	27 30 min Base Pace	28 5 min Warm-Up 30 min MSS 5 min Cool-down

Training Modes are not listed because individuals should continue to progress to upright modes as they can tolerate.
We recommend beginning Interval training on the rower, upright bike or elliptical.
Weight Training can be done on same days as Cardio workouts if necessary.

Month 5

Sun	Mon	Tue	Wed	Thu	Fri	Sat
1	2 60 min Base Pace	3 Weight Training	4 45 min Base Pace	5 45 min Base Pace	6 Weight Training	7 60 min Base Pace
8 Weight Training	9 5 min Warm-Up 5x2 min Intervals 5 min Cool-down 20 min Recovery	5 45 min Base Pace	11 40 min Base Pace	12 Weight Training	13 5 min Warm-Up 40 min MSS 5 min Cool-down	14
15 60 min Base Pace	16 Weight Training	17 5 min Warm-Up 5x2 min Intervals 5 min Cool-down 20 min Recovery	18 45 min Base Pace	19 5 min Warm-Up 5x2 min Intervals 5 min Cool-down 20 min Recovery	20 Weight Training	21 5 min Warm-Up 40 min MSS 5 min Cool-down
22 60 min Base Pace	23 Weight Training	24 5 min Warm-Up 40 min MSS 5 min Cool-down	25 45 min Base Pace	26 5 min Warm-Up 5x2 min Intervals 5 min Cool-down 20 min Recovery	27 Weight Training	28 60 min Base Pace

Training Modes are not listed because individuals should continue to progress to upright modes as they can tolerate.
We recommend beginning Interval training on the rower, upright bike or elliptical.
Weight Training can be done on same days as Cardio workouts if necessary.



POTS Optional Extended Training Program

Month 6

Sun	Mon	Tue	Wed	Thu	Fri	Sat
1 Weight Training	2 45 min Base Pace	3 45 min Base Pace	4 45 min Base Pace	5 Weight Training	6 5min Warm-Up 40 min MSS 5min Cool-down	7
8 60 min Base Pace	9 Weight Training	10 45 min Base Pace	11 5min Warm-Up 45 min MSS 5min Cool-down	12 45 min Base Pace	13 Weight Training	14 5min Warm-Up 7x2 min Intervals 5min Cool-down 20 min Recovery
15 Weight Training	16 5min Warm-Up 5x3 min Intervals 5min Cool-down 20 min Recovery	17 45 min Base Pace	18 5min Warm-Up 45 min MSS 5min Cool-down	19 45 min Base Pace	20 5min Warm-Up 5x3 min Intervals 5min Cool-down 20 min Recovery	21 Weight Training
22 60 min Base Pace	23 Weight Training	24 5min Warm-Up 10x2 min Intervals 5min Cool-down 20 min Recovery	25 45 min Base Pace	26 5min Warm-Up 45 min MSS 5min Cool-down	27 Weight Training	28 60 min Base Pace
29 Weight Training	30 5min Warm-Up 45 min MSS 5min Cool-down	31 45 min Base Pace	Weight Training	45 min Base Pace	45 min Base Pace	

Training Modes are not listed because individuals should continue to progress to upright modes as they can tolerate.
We recommend beginning Interval training on the rower, upright bike or elliptical.
Weight Training can be done on same days as Cardio workouts if necessary.

Above is Levine et al. training protocol schedule. See source #27 for the full print out including various pieces of patient and practitioner education and considerations to be aware while working through this program. [26, 27]

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