**Ehlers-Danlos Syndrome**

Ehlers-Danlos Syndrome (EDS) is a rare inherited connective tissue disorder that affects over 1.5 million people world-wide. EDS consists of six different types with each type having a different genetic defect that causes similar but separate clinical presentations. Previously the types were categorized by numbers but in 2008 the current classification system was adapted to a more descriptive nomenclature.1 The six types of EDS are: classic, hypermobility, vascular, kyphoscoliosis, arthrochalasia, and dermatosparaxis. The first three types listed are most common and will be the focus of this paper; while the last three are extremely rare and less defined.1,2 The types are determined by genetic basis, family history, clinical presentation, and differential diagnosis.1 The hypermobility type of EDS is the most common with some reported incidence rates as high as 1 in 5000 people.1 Of the three most common EDS types, vascular EDS is least common (about 4 percent of all EDS cases) but by far the most dangerous. Vascular EDS can be life threatening due to the potential for vessel or organ rupture.3

The most common clinical presentation of EDS is fragile tissue, hyperextensibility of the skin and symptomatic joint hypermobility. In all forms of EDS, at least one of those symptoms is typical. Some other common symptoms include: unexplained rupture of vessels or hollow organs, easy or excessive bruising and bleeding, multiple subluxations or dislocations, translucent skin, slow wound healing, and atrophic scarring.1,4 Individuals with EDS are also more likely to experience bowel disorders (e.g. irritable bowel syndrome and gastritis), cardiovascular difficulties (e.g. autonomic dysfunction and hypotension) which are treatable once identified.3

Diagnosis of EDS should be considered when various symptoms occur without explanation and in the absence of other health diagnoses. For the classic type of EDS the major diagnostic criteria include: “skin hyperextensibility, widened atrophic scars (manifestation of tissue fragility), and joint hypermobility”.2 Some minor diagnostic criteria include: muscle hypotonia, bruising, tissue fragility (e.g. hiatal hernia or anal prolapse), subcutaneous spheroids (calcified fat lobules), and molluscoid pseudotumors (thickened, scar, skin lesions typically on the elbows or knees).2,4 The major criteria for the hypermobility type of EDS include: “skin involvement (hyperextensibility and/or smooth, velvety skin) and generalized joint hypermobility.” The minor diagnostic criteria include family history, chronic pain in the joints or extremities, and repeat joint subluxations or dislocations.2 Joint hypermobility is the most common sign, with frequent occurrences at the “shoulder, patella, and temporomandibular joints.”2 The major diagnostic criteria for the vascular type of EDS include: “thin, translucent skin; arterial/intestinal/uterine fragility or rupture; extensive bruising; and characteristic facial appearance (thin eyes, nose, and face, and prominent eyes)”.1,2 Minor criteria include features such as: ruptures in tendons or muscles; family history paired with a sudden death of a relative; hypermobility in small joints (typically only the hands); clubfoot; pneumothorax; gingival recession; and varicose vein onset early in life.2 A diagnosis of vascular EDS is highly likely when two or more major criteria are present. Further genetic testing is highly recommended due to the nature of the disease.2

The most common form of screening for classic and hypermobility EDS is via use of the Beighton Scale. This 9 point scale assesses joint hypermobility and a score of 5/9 or greater indicates hypermobility.2 The total score is obtained by the following 5 tests: “1) passive dorsiflexion of the little fingers beyond 90°; 2) passive apposition of the thumbs to the flexor aspect of the forearm; 3) hyperextension of the elbows beyond 10°; 4) hyperextension of the knees beyond 10°; 5) forward flexion of the trunk with knees fully extended so that the palms of the hand rest flat on the floor”.2 One point is given for each extremity that tests positive in tests 1-4 and 1 point for a positive test in the last test.2 This test alone isn’t enough for a diagnosis of EDS, (particularly in children, who are naturally more hypermobile than adults) but must be factored into the entire patient presentation.3

 Additional testing can be done based on additional symptom presentation and clinical testing. Skin hyperextensibility should be measured by pulling up until resistance is felt in the skin.2 This can be more difficult to assess in individuals with higher amounts of subcutaneous fat.2 The best areas to measure are those with lack of open wound or scarring and less subcutaneous fat. The volar side of the forearm is a common testing site and not every site tested must test positive for EDS .3 In individuals with EDS, bruising occurs easily and often repeats in the same areas with an extended healing process.2 In addition to bruising, intense scarring can occur due to tissue fragility. Wound healing is slow and the resultant scars can appear large and discolored.2 Mitral valve prolapse is common in individuals with ESD, as well as proximal aortic dilation (though less common) which can be progressive. These can be diagnosed with echocardiography, MRI or CT scan. Chronic limb and joint pain can be common though hard to localize specific anatomical locations if radiography appears normal.2 Tender points occur in some individuals. These can be identified when pain is elicited when 4kg or less of pressure is applied to a point on the skin when palpated with only a finger or thumb.2

EDS is typically due to alterations in the genetic structure of certain genes. In many of the types of EDS, inheriting a single copy of the abnormal gene is enough for the disease to be expressed in the individual.1 Those who inherit a copy of the gene from both parents typically develop a severe or fatal form of the disease.1 For the classic type of EDS, the affected genes are typically COL5A1 and COL5A2. These genes reside in type V collagen molecules. The mutation in the genes causes an adverse reaction with type I collagen tissues during collagen fibrillogenesis.1 This can negatively impact formation of skin, ligaments, bones, and any connective tissue.1 For the hypermobility type of EDS the specific gene mutation has not been identified. Genetic testing is available for all types of EDS except for the hypermobility type.3 Instead it is often diagnosed by clinical presentation and family history. Additionally, this could contribute to the difficulty differentiating hypermobility EDS from joint hypermobility syndrome (JHS).5 There is controversy over whether the two diagnostic labels should become one due to the overwhelming similarities between the diagnoses.5 Finally, the vascular type typically occurs to a mutation in COL3A1 a gene in type III procollagen.1 While most EDS types can be identified clinically it’s beneficial that genetic testing can be utilized for diagnosis confirmation when clinical diagnosis is in doubt.4

Due to the variety in EDS subtypes, there are a plethora of differential diagnoses that should be considered when EDS is suspected. These diagnoses can present similarly to EDS but require different treatment methods. Some common conditions that are mistaken for EDS are: osteogenesis imperfecta, Marfan syndrome, Loeys–Dietz syndrome, skeletal dysplasias, mucopolysaccharidoses, cutis laxa, gastrointestinal entities, pseudoxanthoma elasticum, ullrich congenital muscular dystrophy, occipital horn syndrome, and bethlem myopathy.4,6,7 Individuals with EDS commonly have chronic pain and fatigue which are also major factors in fibromyalgia.8 Although rare, when looking at children’s skin (especially in those that have bruising), child abuse should be also considered as a possible differential diagnosis to EDS.2

Due to the gene mutation that occurs in the connective tissue there are various pathophysiologic changes that occur in the bones, tendons, ligaments, and skin in those with Ehlers-Danlos Syndrome. Because EDS is a disease that primarily affects the connective tissue, previously it was thought that bone wasn’t affected as part of the disease process. However, now researchers agree that that’s not the case. Individuals with EDS tend to have lower bone mineral density (LBD) than those without EDS.3 Additionally, one study found that those with EDS were ten times more likely to have experienced a fracture (86.9%) than the control group (8.7%).9 Many individuals with EDS are diagnosed at a young age and advised to avoid strenuous activity and contact sports to avoid injury.9 This reduced exercise could result in decreased BMD and lead to further injury creating a feed-forward negative situation. Additionally, joint hypermobility can be associated with decreased joint proprioception. Lack of body awareness in space and increased sway leads to increased risk for falls and thus increased risk for fracture.9 When diagnosed, individuals with EDS should consider getting a dual energy x ray absorptiometry (DEXA) scan to assess their bone mineral density, especially in the presence of other risk factors.3

Subluxations and dislocations occur often in individuals with EDS and repeated trauma at the joints commonly leads to degenerative joint disease.8 Other tissues such as tendon and ligaments can be easily torn or ruptured with normal activity or become lax and unable to provide joint stability.8 Skin is largely affected in every type of EDS due to its large collagen content and the collagen gene mutation in EDS. Skin is either very thin and translucent (vascular EDS) or hyperextensible (classic and hypermobility types). In the vascular type, skin is less likely to hyperextend but is much more fragile.4 This can lead to poor wound healing, spontaneous cuts and tears, wound dehiscence and wide, thick scars.8 All tissue that contains collagen can be affected depending on the type of EDS and its physical manifestations.

Medications used by those with EDS are primarily used for pain control. Chronic pain is common and as a result most medications used are to minimize pain rather than address individual impairments. Non-prescription acetaminophen and NSAIDs are commonly suggested in the literature.8 Topical lidocaine can be used for localized areas but not always practical for individuals with EDS, as their pain is often widespread.8 Skeletal muscle relaxants can be combined with one of the above pain medications to decreased myofascial spasm. Opioids can be utilized for myofascial and neuropathic pain; however, these should be used as a last resort. If necessary, it’s recommended that the above pain medications are still used to minimize the overall amount of opioids needed.8 Additionally, some research mentions corticosteroid injections as a treatment for pain and acute inflammation; however, individuals should be extremely cautious due to the significant tissue effects caused by these injections to already fragile connective tissue.8 An alternative that might provide similar benefit without the punitive side effects is dry needling.8

Surgical treatments are necessary in some EDS types more than others. Individuals with vascular EDS might require surgery as a life-saving intervention after organ or bowel rupture and to stop severe bleeding after arterial rupture.6 Especially in those with vascular EDS, the surgical intervention could easily lead to further complications due to tissue fragility. Those with vascular EDS benefit from working with a surgeon who is aware of the diagnosis and associated complications.6 Swift response should be utilized when surgically repairing a bowel rupture. If prompt intervention occurs, the risk for death is low and the individual typically makes a full recovery. Despite this individuals are likely to have reoccurring tears around the original site and thus require repeated surgeries.6 As a result, some patient opt to undergo prophylactic measures, such as a total colectomy to avoid repeat complications and surgery.6

 In those with classic or hypermobility EDS, surgical options are typically orthopedic in nature and include: “joint debridement, tendon relocations, capsulorraphy, and arthroplasty” as well as relocations for joint subluxations or dislocations.8 Those with classic and hypermobility EDS normally don’t have increased risk of post-operative skin and tissue complications like those with vascular EDS. However, the results of orthopedic surgeries (e.g. patient satisfaction, pain reduction, joint stabilization, etc.) are typically less than those without EDS.8 More conservative treatment methods (bracing, physical therapy, and activity modification) are usually more beneficial and should be attempted first.8

Physical therapy can be incredibly beneficial to individuals with EDS, particularly those with the hypermobility and classic types. One example is a physical therapist led exercise program that focused on increasing strength and muscular endurance, decreasing pain, and decreasing kinesiophobia. The exercises prescribed included: squats, seated rowing with a theraband, sit-ups on a physioball, side-lying hip abduction, glute bridge on physioball, wall push-ups, and various back and core exercises.10 Upon completion of the 12 week combination clinic and home exercise program, participants showed significant improvement in strength and endurance as well as improved performance of daily activities and decreased kinesiophobia.10

Physical therapy modalities, such as “heat, cold, massage, ultrasound, electrical stimulation, biofeedback, and conscious relaxation” can be used to decrease pain but physical therapists should work to facilitate less passive pain management techniques.8 Pelvic floor physical therapy can be beneficial for this patient population. Transvaginal massage or ultrasound may improve dyspareunia and decrease abdominal, back and lower-extremity pain.8

In terms of specific strengthening activities, rather than a focus on resistance, exercise progression should focus on increasing time, frequency and repetitions.8 Once an individual has reached the point of extreme pain and instability due to their joint laxity, it can be an incredibly slow process (months or years) to reverse these changes using resistance training.3 Low resistance exercise should be performed and high-impact and collision activities should be avoided.3 For vascular EDS, there is no evidence of detrimental results for moderate-activity exercise.6 Individuals should just use caution when selecting and performed physical activity.

Bracing and assistive devices can be beneficial, particularly for those who have joint hypermobility to help provide external stability. Common problematic joints such as the knee and ankle are more easily braced compared to the more challenging hips and shoulders.8 Small joint instability and the wrists and hands can be easily braced and ring splints to stabilize interphalangeal joints can be customized by hand therapists. For those with headaches or cervical spine pain, a soft collar can be used.8 For those with fragile skin, protective padding can be worn to avoid skin tears.7 If an individual with EDS is having difficulty ambulating, wheelchairs or scooters can be used. Other assistive devices such as walkers, crutches, or canes should be avoided due to increased stress on the upper-extremities with use.8

One of the most effective methods of symptoms management in those with EDS is activity modification. Patients should be encouraged to avoid any activities that are likely to cause trauma. These include: any impact sports or activities and heavy lifting, either by weight lifting or via household activities.6 In addition, individuals should avoid stretching or extreme end-range positions to minimize joint stress.3 Both physical and occupational therapists are excellent resources for focusing on activity modification and should be utilized by those with EDS.

Preventative measures are the best way to help manage symptoms and prevent more severe complications. Individuals with family history of EDS should see a physician to determine if they could be affected and learn about conservative methods in advance of injury. This is especially important for those with vascular EDS because they could appear asymptomatic initially but spontaneous organ or vessel rupture could lead to life-threatening circumstances.6 Persons with EDS should regularly monitor their blood pressure. In vascular EDS, hypertension could cause increased vascular stress and injury.6 In classic EDS, hypotension could be a sign of autonomic dysfunction.7 For both extremes, early intervention is vital to minimizing resultant complications. If possible, blood pressure abnormalities should be treated holistically to avoid side effects from medications.3

Although rare, Ehlers-Danlos Syndrome and its resultant symptoms can cause a negative impact on an individual’s quality of life. If possible, it’s best to identify EDS early and seek treatment. This allows individuals to take preventative measures to protect themselves from injury, sickness or even death. It’s important to try to minimize pain and fatigue with conservative approaches to minimize further side-effects from medications or surgery. Some lifestyle recommendation to improve quality of life include: “regular, aerobic fitness (with strengthening, gentle stretching, and proprioception exercises)”; weight control management; relaxation exercises; regular eye appointments; ergonomic posture during sleep and daily activity; and avoiding high impact sports, lifting heavy objects, large meals, hard foods (due to excessive jaw movements, bladder irritants (e.g., coffee and citrus), and nicotine.11 Receiving early treatment from an experienced interdisciplinary team and making positive lifestyle changes, can help individuals with Ehlers-Danlos Syndrome better mitigate their impairments and maximize their quality of life.

**References**

1. Pauker SP, Stoler J. Clinical manifestations and diagnosis of Ehlers-Danlos syndromes. *Wolters Kluwer Heal*. 2015. http://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-ehlers-danlos-syndromes#H30603900.

2. Beighton P, De Paepe A, Steinmann B, Tsipouras P, Wenstrup RJ. Ehlers-Danlos syndromes: revised nosology, Villefranche, 1997. Ehlers-Danlos National Foundation (USA) and Ehlers-Danlos Support Group (UK). *Am J Med Genet*. 1998;77(1):31-37. http://www.ncbi.nlm.nih.gov/pubmed/9557891. Accessed December 1, 2015.

3. Medical Resource Guide. *Ehlers-Danlos Natl Found*. 2010. http://ednf.org/. Accessed November 16, 2015.

4. Sobey G. Ehlers-Danlos syndrome: how to diagnose and when to perform genetic tests. *Arch Dis Child*. 2015;100(1):57-61. doi:10.1136/archdischild-2013-304822.

5. Tinkle BT, Bird HA, Grahame R, Lavallee M, Levy HP, Sillence D. The lack of clinical distinction between the hypermobility type of Ehlers-Danlos syndrome and the joint hypermobility syndrome (a.k.a. hypermobility syndrome). *Am J Med Genet A*. 2009;149A(11):2368-2370. doi:10.1002/ajmg.a.33070.

6. Pepin MG, Murray ML, Byers PH. Vascular Ehlers-Danlos Syndrome. November 2015. http://www.ncbi.nlm.nih.gov/books/NBK1494/.

7. Malfait F, Wenstrup R, Paepe A De. Ehlers-Danlos Syndrome, Classic Type. August 2011. http://www.ncbi.nlm.nih.gov/books/NBK1244/.

8. Levy HP. Ehlers-Danlos Syndrome, Hypermobility Type. September 2012. http://www.ncbi.nlm.nih.gov/books/NBK1279/.

9. Dolan AL, Arden NK, Grahame R, Spector TD. Assessment of bone in Ehlers Danlos syndrome by ultrasound and densitometry. *Ann Rheum Dis*. 1998;57(10):630-633. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1752482&tool=pmcentrez&rendertype=abstract.

10. Bathen T, Hångmann AB, Hoff M, Andersen LØ, Rand-Hendriksen S. Multidisciplinary treatment of disability in ehlers-danlos syndrome hypermobility type/hypermobility syndrome: A pilot study using a combination of physical and cognitive-behavioral therapy on 12 women. *Am J Med Genet A*. 2013;161A(12):3005-3011. doi:10.1002/ajmg.a.36060.

11. Castori M. Ehlers-danlos syndrome, hypermobility type: an underdiagnosed hereditary connective tissue disorder with mucocutaneous, articular, and systemic manifestations. *ISRN Dermatol*. 2012;2012:751768. doi:10.5402/2012/751768.