BIO210 Anatomy & Physiology and Disease Assignment

# Hypermobile Ehlers-Danlos Syndrome (hEDS): A Review

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Submitted to Dr. Krupa Patel

Friday, August 7th, 2020.

## Introduction

The Ehlers-Danlos Syndromes (EDS) are a group of heritable connective tissue disorders (HCTDs), each with unique genetic causes, phenotypes, and frequencies (Malfait et al., 2017). EDS has existed since at least 400 B.C., when it was first described by Hippocrates (Beighton et al., 2012). The most common type of EDS is also the most common HCTD among humans (with an estimated 255 million people affected worldwide), and it is called hypermobile Ehlers-Danlos Syndrome (hEDS) (Tinkle et al., 2017). hEDS is characterized primarily by connective tissue laxity, and since connective tissue is ubiquitous in the body, symptoms can involve nearly every organ system and tend to vary in type, number, and severity from one person to another (Tinkle et al., 2017). However, some of the hallmark symptoms include symptomatic joint hypermobility, pain, skin abnormalities, and tissue fragility (Malfait et al., 2017). Although hEDS is common (Tinkle et al., 2017) and often severe (Copetti et al., 2019), it is under-diagnosed (Hakim et al., 2005) and "largely neglected" (Kazkaz & Grahame, 2018, p. 256), which causes people with hEDS to experience "unnecessary suffering" (Kazkaz & Grahame, 2018, p. 256).

While true, these statements underestimate how severely people with hEDS often suffer. I have sat in shock and sadness while news reporters have announced the imprisonment of yet another Canadian physician specializing in hEDS who abused their patients, or the acquittal of yet another perpetrator of child abuse whose lawyers blamed their child's injuries on brittle bones due to hEDS, even though there is absolutely no scientific evidence that hEDS predisposes babies to fractures (Tinkle, 2020; Rolfes et al., 2019; Shur, 2019). I know people with hEDS who sought help from doctors for decades before finally receiving an hEDS diagnosis, who have nearly died because healthcare professionals mismanaged their condition, and whose health holds them back from leading the life they long for. I wholeheartedly echo one clinician who called EDS "the most neglected disorder in modern medicine" (The Ehlers-Danlos Society, 2017).

hEDS direly requires increases in research, funding, treatments, and the education of healthcare workers. The first step toward these goals is raising awareness, and I would like to use this assignment as an opportunity to do so. Therefore, by engaging with this paper, the reader becomes part of the solution. Moreover, given the high prevalence yet under-diagnosis of hEDS, the reader may be equipping themselves to identify this condition in someone they know.

Cause/Effect

hEDS is classified as a genetic disorder with an autosomal dominant inheritance pattern, but the genetic mutation(s) that cause(s) this disorder have not yet been determined (Malfait et al., 2017). This may be partly because hEDS is genetically heterogeneous (Malfait et al., 2017) and/or affected by gene-environment interactions (Martin, 2019). Currently, the cause of hEDS is presumed to involve one or more mutated genes that code for extracellular matrix (ECM) proteins (Tinkle et al., 2017). The ECM is the major component of connective tissue and it primarily consists of collagen fibers (which are strong and resist stretching), elastic fibers (which recoil to their former lengths after stretching), reticular fibers (which form a supporting network called a stroma), and a fluid called ground substance (Martini et al., 2018). The ECM's functions include the establishment of a structural framework, transportation of substances, protection of organs, support of other tissues, storage of energy, and immune response (Martini et al., 2018).

hEDS is thought to be caused by the following pathomechanism: genetic mutation(s) → structural/functional alterations to the ECM → fragility, laxity, decreased tensile strength, mechanical failure, and rupture of connective tissue → loss of integrity of skin, joints, organs, etc. → multisystemic symptoms (Chiarelli et al., 2019; Kazkaz & Grahame, 2018). Table 1 summarizes the results of recent studies of hEDS patients' dermal fibroblasts (cells within the dermis of the skin that create and maintain connective tissue (Martini et al., 2018)), which have provided insight into possible defects of the ECM and their effects on phenotype (Chiarelli et al., 2019).

**Table 1.** The major abnormalities in the dermal fibroblasts of hEDS patients (Chiarelli et al., 2019).

| Structural/Functional Anomalies in hEDS Dermal Fibroblasts | Potential Contribution(s) to the hEDS Phenotype |
|---|---|
| Disorganization of collagen fibers and dysregulated expression of genes encoding several ECM proteins, including elastic fibers. | Disorganization of the ECM. |
| Increased levels of enzymes that degrade the ECM. | Inhibition of the ECM's functions. |
| Dysregulated genes encoding adhesion molecules, e.g. desmosomes*. | Impaired epithelial integrity and tissue architecture. |
| The conversion of fibroblasts to myofibroblasts (muscle-like cells). | Inflammation, digestive dysfunction, osteoarthritis, musculoskeletal pain, and neurological symptoms. |
| Aberrant transcription of several genes. | Inflammatory, pain, and immune responses. |

*__Desmosomes__ interlock the cytoskeletons of epithelial cells, helping them withstand stretching/twisting (Martini et al., 2018).

Since the cause of hEDS is unknown, researchers have only hypothesized (and not yet definitively determined) the relationships between the cause and effects (Chiarelli et al., 2019). One such hypothesis is the pathomechanism described above, and additional hypotheses are listed in Table 2 (Chiarelli et al., 2019; Kazkaz & Grahame, 2018; Tinkle et al., 2017).

**Table 2.** A summary of the most common symptoms of hEDS and their presumed causes. The lettering system allows the reader to link the symptom in the middle column to the cause in the right-hand column. The lettering system resets with each subsequent row. Sources: [1](Tinkle et al., 2017), [2](Martini et al., 2018), [3](Hakim et al., 2017), [4](Ericson & Wolman, 2017).

| Organ System | A Summary of Some of the Major hEDS Symptoms | Presumed Causes of these Symptoms |
|---|---|---|
| **Musculo-skeletal system** (which can also be separately considered as the muscular and skeletal systems) | a) Joint hypermobility and instability, including in the entire spine[1]<br>b) Subluxations (partial dislocations) and complete dislocations, most commonly of the shoulders, knees, and ankles[1]<br>c) Iliotibial (IT) band syndrome, where the IT band snaps over the greater trochanter of the femur repetitively[1]<br>d) Temporomandibular joint dysfunction (TMD)[1]<br>e) Postural kyphosis (rounded upper back)[1]<br>f) Acquired scoliosis (lateral spine curvature)[1]<br>g) Premature aging of the musculoskeletal system[1]<br>h) Osteoarthritis (damage to the articular cartilage of a joint[2])[1] | e) Loose ligaments due to weak connective tissue[1]<br>h) Joint hypermobility/repetitive trauma/ altered mechanics, weak connective tissue[1] |
| **Integumentary System** | a) Skin that is soft, velvety, semi-translucent, hyperextensible, fragile, and/or easily bruised[1]<br>b) Striae (stretch marks)[1]<br>c) Atrophic scars (scars that are sunken into the skin)[1]<br>d) Poor wound healing[1] | |
| **Cardiovascular** | a) Mild dilation of the aorta[1]<br>b) Mitral and tricuspid valve prolapse[1] | b) Connective tissue in chordae tendineae is too weak to provide tension[1,2] |
| **Digestive** | a) Gastroesophageal reflux (stomach acid enters esophagus)[1]<br>b) Irritable bowel syndrome (IBS), bloating, constipation, diarrhea[1] | |
| **Nervous** | <u>Dysautonomia (dysregulation of the autonomic nervous system)[1]:</u><br>a) Orthostatic intolerance (OI) (development of symptoms upon standing)[1]<br>o Postural orthostatic tachycardia syndrome (POTS) (inappropriately rapid heart rate upon standing)[1]<br>o Neurally mediated hypotension (NMH) (rapid decreases in heart rate and blood pressure upon standing)[1]<br>o Secondary neurological symptoms: fatigue, dizziness, fainting, syncope, "brain fog" (memory/concentration issues), digestive problems, etc.[1]<br>b) Dry skin and mucosa, poor temperature regulation, etc.[1] | a) Abnormally elastic arteries (resulting in low blood pressure), abnormal connective tissue in veins (resulting in venous pooling and low blood pressure), the high histamine levels seen in MCAS (which lowers blood pressure and raises heart rate), physical deconditioning (poor physical fitness), etc.[3] |
| **Reproductive** | a) Heavy menstrual bleeding[1]<br>b) Painful intercourse[1]<br>c) Pelvic organ prolapse (bladder, urethra, uterus, vagina, small bowel, or rectum droops down or protrudes out of an orifice)[1]<br>d) Rapid labour and delivery[1] | c) Mechanical failure of the musculotendinous support of these organs due to connective tissue laxity[1] |
| **Urinary** | a) Urinary incontinence (leaking urine)[1]<br>b) Urinary tract infections (UTIs)[1]<br>c) Voiding dysfunction (difficulty emptying the bladder)[1]<br>d) Vesicoureteral reflux (backward flow of urine)[1] | |
| **Lymphatic** | a) Mast cell activation syndrome (MCAS)[1]<br>o caused by increased numbers of mast cells, their mediators (particularly histamine), or both[1]<br>o can cause flushing, hypotension (low blood pressure), asthma, diarrhea, abdominal bloating/cramping, and/or food sensitivities[1] | |
| **N/A** | a) Chronic, widespread musculoskeletal pain[1]<br>b) Nerve pain[1]<br>c) Headaches[1]<br>d) Chronic, debilitating fatigue[1]<br>e) Mental illness (depression, anxiety, eating disorders, suicide)[1] | a) Muscle/tendon/connective tissue spasm/tears, joint injury/swelling[1,4]<br>b) Nerve compression due to laxity[4]<br>c) Poor sleep quality, pain, OI, depression[1]<br>d) Cervical instability, tense muscles, TMD[1] |

Detection

Since the genetic basis of hEDS is still unknown, there is no laboratory test that can confirm or refute a diagnosis (Malfait et al., 2017). Therefore, the diagnosis of hEDS is clinical (Malfait et al., 2017). The most recent diagnostic criteria for hEDS, which were developed by an international EDS consortium in 2017, are summarized in Table 3 (Malfait et al., 2017). A patient can only be diagnosed with hEDS if they meet all three criteria in Table 3 (Malfait et al., 2017). These three diagnostic criteria depend primarily on joint hypermobility, integumentary abnormalities, organ prolapse, positive family history, and chronic pain (Malfait et al., 2017).

One urgently required advancement is the discovery of the genetic cause(s) of hEDS (Malfait et al., 2017). Firstly, the discovery of the genetic cause(s) would allow for diagnoses to be made more accurately and earlier in patients' lives, which would improve patient outcomes while also lowering healthcare costs (McGillis et al., 2019). Researchers are currently working toward the elucidation of the genetic cause(s) of hEDS through a project called Hypermobile Ehlers-Danlos Genetic Evaluation (HEDGE), which aims to genetically test 1000 individuals who meet the criteria described in Table 3 by the end of 2020 (Ritelli & Colombi, 2020).

Another necessary advancement is a revision of the 2017 diagnostic criteria described in Table 3 to make them more sensitive, specific, and objective (Malfait et al., 2017). These criteria were primarily developed to create a homogeneous group of patients for the purposes of further research; however, using a "one-size-fits-all" model for a condition that is phenotypically diverse has been problematic, and has caused 85% of previously-diagnosed hEDS patients to no longer meet the new diagnostic criteria (Tinkle et al., 2017; McGillis et al., 2019). One likely reason why the 2017 criteria capture so few symptomatic hEDS patients is because they exclude many extremely common symptoms, such as gastrointestinal disease (which is present among 90% of patients) (McGillis et al., 2019). Another part of the problem is that the Beighton scale is a poor measure of hypermobility, since it does not assess the most commonly affected joints among hEDS patients (shoulder, neck, pelvis, hip, ankle, and foot) and is affected by sex, ethnicity, physical activity, and muscle tightness (Palmer et al., 2020; Alsiri et al., 2018). One suggested novel assessment of joint hypermobility is an objective measure of excess glenohumeral abduction (Cypel, 2019).

**Table 3.** The diagnostic criteria for hEDS, as defined by the 2017 classification system (Malfait et al., 2017).

**CRITERION #1: Generalized Joint Hypermobility (GJH)**

The Beighton score must be in one of the following ranges: ≥6 for pre-pubertal children and adolescents, ≥5 for pubertal men and women up to the age of 50, and ≥4 for those >50 years of age. The Beighton score is measured by a goniometer, awards points to each side of the body independently, is scored out of a max. possible total of 9 points, and consists of the following metrics:

- Hyperextension by >90º of the metacarpal-phalangeal joint of the fifth finger when the palm and forearm are resting on a level surface and the elbow is at a 90º angle.
- Passive movement of the pollex to touch the anterior surface of the forearm when the arm is outstretched and pronated.
- Hyperextension of the elbow by >10º in the anatomical position.
- Hyperextension of the knee by >10º when standing.
- Bending forward to place both hands flat on the floor in front of the feet when standing with straight legs and feet together.

If the Beighton score is 1 point below the appropriate range, the answers to at least two of the following questions on the five-point questionnaire (5PQ) must be yes:

- "Can you now (or could you ever) place your hands flat on the floor without bending your knees?" (Malfait et al., 2017, p. 17).
- "Can you now (or could you ever) bend your thumb to touch your forearm?" (Malfait et al., 2017, p. 17).
- "As a child, did you amuse your friends by contorting your body into strange shapes or could you do the splits?" (Malfait et al., 2017, p. 17).
- "As a child or teenager, did your shoulder or kneecap dislocate on more than one occasion?" (Malfait et al., 2017, p. 17).
- "Do you consider yourself 'double-jointed'?" (Malfait et al., 2017, p. 17).

**CRITERION #2: At least 2 of the following 3 features must be present**

Feature A: At least 5 of the following 12 features must be present

- Skin that is unusually soft or velvety.
- Skin that hyperextends by >1.5 cm when the cutaneous and subcutaneous layers on the anterior surface of the non-dominant forearm are pinched and lifted.
- Striae that cannot be explained by historical changes in weight.
- Piezogenic papules on both heels.
- Multiple recurrent abdominal hernias.
- At least two atrophic scars.
- Prolapse of the pelvic floor, rectum, and/or uterus without other pre-disposing conditions.
- Dental crowding and a high-arched or narrow palate.
- At least one of the following measures of arachnodactyly:
  - Positive Steinberg sign on both sides of the body, meaning that the tip of the pollex is visible medial to the fifth phalanx when it is held in a clenched hand.
  - Positive Walker sign on both sides of the body, meaning that the pollex and fifth finger overlap when they are curled around the opposite wrist.
- A ratio of arm span to height ≥1.05.
- Mild or greater mitral valve prolapse (MVP), as seen on an echocardiogram.
- Aortic root dilatation where the Z-score >+2.

Feature B: At least one first-degree relative must meet all three hEDS diagnostic criteria.

Feature C: At least 1 of the following 3 musculoskeletal complications must be present

- Daily musculoskeletal pain in at least two limbs for ≥3 months.
- Chronic pain that has been widespread throughout the body for ≥3 months.
- At least one of the following measures of joint instability:
  - ≥3 atraumatic dislocations of a single joint or ≥2 atraumatic dislocations of 2 different joints on different dates.
  - Atraumatic joint instability at ≥2 sites.

**CRITERION #3: All of the following requirements must be met**

- The skin must not be unusually fragile.
- The patient must not have other connective tissue disorders (heritable or acquired).
- Joint hypermobility must not be explainable by alternative diagnoses such as hypotonia and/or laxity of connective tissue.

Treatment/Therapies

Since there is no cure for hEDS (or any subtype of EDS), hEDS can only be managed via the prevention of complications, the minimization of chronic symptoms, and the treatment of acute symptoms (Tinkle et al., 2017). It is important to note that there are two caveats in the following summary of management strategies for hEDS. Firstly, where an organ system or symptom is not addressed, no treatment protocols specific to hEDS have yet been established. Secondly, since a relatively small amount of research has been conducted on hEDS to date, it is difficult to acquire statistics on their efficacies (Tinkle et al., 2017).

Musculoskeletal symptoms should be managed as conservatively as possible, and interventions such as physiotherapy, education, rest, ice, compression, elevation, and pain management should be exhausted before surgery is considered (Tinkle et al., 2017; Engelbert et al., 2017). This is because surgery tends to be much less effective and higher risk among hEDS patients than in the general population (Engelbert et al., 2017).

Although cardiovascular complications are possible, they are relatively rare; therefore, electrocardiograms should only be conducted if symptoms arise, and there is no need to repeat them on a routine basis otherwise (Hakim et al., 2017).

For the management of digestive symptoms, it is suggested for patients to try the low FODMAP diet, which minimizes the amount of Fructose, Oligosaccharides, Disaccharides, Monosaccharides, and Polyols that the patient consumes (Fikree et al., 2017). The evidence in favour of this treatment is that many of the digestive symptoms which hEDS patients experience fall under the category of IBS, and the low FODMAP diet is known to be efficacious in the management of IBS (Fikree et al., 2017).

Symptoms of Dysautonomia and its sub-types can usually be managed by a combination of exercise, increased fluid and sodium intake (to increase blood volume), weekly infusions of saline (to increase blood volume), compression stockings (to minimize the pooling of blood in the lower limbs), and medications (Hakim et al., 2017). The two first-line drugs are fludrocortisone (a steroid that promotes sodium reabsorption and thereby increased blood pressure) and midodrine (a vasoconstrictor) (Hakim et al., 2017). Fludrocortisone is prescribed for Dysautonomia more frequently than midodrine is, even though fludrocortisone is not FDA-approved for this condition (and midodrine is), fludrocortisone has more dangerous potential side effects than midodrine (most

notably congestive heart failure), and fludrocortisone is associated with a higher risk of hospitalization than midodrine (Grijalva et al., 2017).

MCAS symptoms are typically treated by one or more of the following medications: $H_1$ antihistamines, $H_2$ antihistamines, sodium cromoglicate, ketotifen, leukotriene receptor blockers, and steroids (Seneviratne et al., 2017). New-generation $H_1$ antihistamines are typically the first class of drugs on this list to be prescribed (Seneviratne et al., 2017). These medications inhibit $H_1$ receptors in cells throughout the body, which dampens the ability of these receptors to be activated by histamine, and which decreases the adverse symptoms associated with mast cells over-producing histamines (Nurmatov et al., 2015). However, evidence supporting the efficacy of $H_1$ antihistamines in managing MCAS symptoms is extremely scarce, and it is based almost entirely on a single trial of 33 adults with MCAS but not comorbid hEDS (Nurmatov et al., 2015).

Although research has demonstrated that well over 90% of hEDS patients live with severe chronic pain which tends to gradually increase over time, little research has been conducted on pain management in hEDS (Chopra et al., 2017). To put this into perspective, after reading through more than 100 papers on hEDS, the author of the present paper only managed to find a *single* article evaluating the efficacy of a medication in the management of pain among hEDS patients, and this article only included *2* hEDS patients in its analysis (Brown & Stinson, 2004). Therefore, despite a lack of research on the topic, it is recommended that pain is managed in hEDS patients by physiotherapy, exercise, cognitive behavioural therapy, and medications (such as non-steroidal anti-inflammatory drugs (NSAIDS), opioids, anti-depressants, and topical or injected lidocaine) (Chopra et al., 2017). However, most of these medications have detrimental long-term side effects; for instance, NSAIDS worsen MCAS, opioids exacerbate gastrointestinal issues, and anti-depressants aggravate dysautonomia (Chopra et al., 2017). hEDS patients tend to fall into one of two categories: they either take no pain-control medications because they have tried many but all have been ineffective/symptom-triggering, or they have slowly transitioned to progressively stronger medications over time (Bénistan & Gillas, 2020).

Status

The medical community is nowhere near having hEDS under control. Firstly, given that there is no genetic test for hEDS and the clinical diagnostic criteria are inaccurate, hEDS patients typically do not receive a correct diagnosis until late in life, which causes them to experience prolonged hospitalizations and undergo healthcare procedures that are at best unnecessary and at worst harmful, thereby increasing their suffering and the cost of healthcare (McGillis et al., 2019; Thi Dang et al., 2019). Secondly, since there is extremely limited research on the efficacy of treatments or therapies targeted toward hEDS patients, they typically live with symptoms that are not even close to being under control, and their quality of life is extremely poor (Bénistan & Gillas, 2020). Even with treatment, more than 90% of hEDS patients experience chronic pain (Bénistan & Gillas, 2020), more than 90% experience severe gastrointestinal symptoms (McGillis et al., 2019), more than 50% experience uncontrolled dysautonomia (McGillis et al., 2019), more than 65% live with comorbid mental illness (McGillis et al., 2019), more than 65% have a mobility disability (Kalisch et al., 2019), and 22% of hEDS patients evaluated in one study reported having attempted suicide at age 25 or younger (Bénistan & Gillas, 2020). hEDS patients typically report that healthcare professionals do not understand them, their lives are extremely restricted, there is a social stigma that accompanies their condition, they struggle and fail to keep up with others who do not have hEDS, and they struggle to gain control over their health and its impacts on their lives (Bennett et al., 2019).

In the future, it is projected that the genetic cause(s) of hEDS will likely be elucidated, possibly even through the ground-breaking HEDGE project (Tinkle et al., 2017; Ritelli & Colombi, 2020). If the pathomechanism of hEDS is fully elucidated, more targeted treatments may be developed (Chiarelli et al., 2019). In the interim, it would be extremely beneficial if large-scale, well-controlled studies were conducted to evaluate and compare the efficacies of existing management strategies for hEDS (Tinkle et al., 2017). Additionally, it is anticipated that as physicians are increasingly educated about hEDS, the rate at which patients are diagnosed will increase and the age at which they are diagnosed will decrease, which will decrease suffering due to inappropriate treatment (Kalisch et al., 2019).

## References

Alsiri, N., Al-Obaidi, S., Asbeutah, A., Almandeel, M., & Palmer, S. (2018). The impact of hypermobility spectrum disorders on musculoskeletal tissue stiffness: an exploration using strain elastography. *Clinical Rheumatology*, *38*(2019), 85-95. https://doi.org/10.1007/s10067-018-4193-0

Beighton, P., Grahame, R., & Bird, H. (2012). *Introduction to hypermobility*. In: Hypermobility of Joints. Springer.

Bénistan, K., & Gillas, F. (2020). Pain in Ehlers-Danlos Syndromes. *Joint Bone Spine 87*(3), 199-201. https://doi.org/10.1016/j.jbspin.2019.09.011

Bénistan, K., & Martinez, V. (2019). Pain in hypermobile Ehlers-Danlos syndrome: New insights using new criteria. *American Journal of Medical Genetics Part A, 179A*(2019), 1226-1234. https://doi.org/10.1002/ajmg.a.61175

Bennett, S. E., Walsh, N., Moss, T., & Palmer, S. (2019). The lived experience of Joint Hypermobility and Ehlers-Danlos Syndromes: a systematic review and thematic synthesis. *Physical Therapy Reviews 24*(1-2), 12-28. https://doi.org/10.1080/10833196.2019.1590674

Brown, S. C., & Stinson, J. (2004). Treatment of pediatric chronic pain with tramadol hydrochloride: Siblings with Ehlers-Danlos Syndrome – Hypermobility Type. *Pain Research and Management 9*(4), 209-211. https://doi.org/10.1155/2004/370915

Chopra, P., Tinkle, B., Hamonet, C., Brock, I., Gompel, A., Bulbena, A., & Francomano, C. (2017). Pain Management in the Ehlers-Danlos Syndromes. *American Journal of Medical Genetics Part C, 175C*(2017), 212-219. https://doi.org/10.1002/ajmg.c.31554

Copetti, M., Morlino, S., Colombi, M., Grammatico, P., Fontana, A., & Castori, M. (2019). Severity classes in adults with hypermobile Ehlers-Danlos syndrome/hypermobility spectrum disorders: a pilot study of 105 Italian patients. *Rheumatology, 58*(10), 1722-1730. https://doi.org/ 10.1093/rheumatology/kez029

Cypel, D. (2019). Gleno-humeral abduction measurement in patients with Ehlers-Danlos syndrome. *Orthopaedics & Traumatology: Surgery & Research, 105*(2019), 287-290. https://doi.org/10.1080/09638288.2017.1390695

Engelbert, R. H. H., Juul-Kristensen, B., Pacey, V., De Wandele, I., Smeenk, S., Woinarosky, N., Sabo, S., Scheper, M. C., Russek, L., & Simmonds, J. V. (2017). The Evidence-Based Rationale for Physical Therapy Treatment of Children, Adolescents, and Adults Diagnosed with Joint Hypermobility Syndrome/Hypermobile Ehlers-Danlos Syndrome. *American Journal of Medical Genetics Part C, 175C*(2017), 158-167. https://doi.org/10.1002/ajmg.c.31545

Ericson Jr., William B., & Woman, R. (2017). Orthopaedic Management of the Ehlers-Danlos Syndromes. *American Journal of Medical Genetics Part C, 175C*(2017), 188-194. https://doi.org/10.1002/ajmg.c.31551

Fikree, A., Chelimsky, G., Collins, H., Kovacic, K., & Aziz, Q. (2017). Gastrointestinal Involvement in the Ehlers-Danlos Syndromes. *American Journal of Medical Genetics Part C, 175C*(2017), 181-187. https://doi.org/10.1002/ajmg.c.31546

Grijalva, C. G., Biaggioni, I., Griffin, M. R., & Shibao, C. A. (2017). Fludrocortisone Is Associated With a Higher Risk of All-Cause Hospitalizations Compared with Midodrine in Patients with Orthostatic Hypotension. *Journal of the American Heart Association 6*(1), e006848. https://doi.org/10.1161/JAHA.117.006848

Hakim., A. J., Grahame, R., Norris, P., & Hopper, C. (2005). Local anaesthetic failure in joint hypermobility syndrome. *Journal of the Royal Society of Medicine, 98*(2), 84-85. https://doi.org/10.1258/jrsm.98.2.84

Hakim, A., O'Callaghan, C., De Wandele, I., Stiles, L., Pocinki, A., & Rowe, P. (2017). Cardiovascular Autonomic Dysfunction in Ehlers-Danlos Syndrome – Hypermobile Type. *American Journal of Medical Genetics Part C, 175C*(2017), 168-174. https://doi.org/10.1002/ajmg.c.31543

Kalisch, L., Hamonet, C., Bourdon, C., Montalescot, L., de Cazotte, C., & Baeza-Velasco, C. (2019). Predictors of pain and mobility disability in the hypermobile Ehlers-Danlos syndrome. *Disability and Rehabilitation*, Article in Press. https://doi.org/10.1080/09638288.2019.1608595

Kazkaz, H., & Grahame, R. (2018). The rheumatological heritable disorders of connective tissue. *Medicine, 46*(4), 256-260. https://doi.org/10.1016/j.mpmed.2018.01.004

Malfait, F., Francomano, C., Byers, P., Belmont, J., Berglund, B., Black, J., Bloom, L., Bowen, J. M., Brady, A. F., Burrows, N. P., Castori, M., Cohen, H., Colombi, M., Demirdas, S., De Backer, J., De Paepe, A., Fournel-Gigleux, S., Frank, M., Ghali, N., … Tinkle, B. (2017). The 2017 International Classification of the Ehlers-Danlos Syndromes. *American Journal of Medical Genetics Part C, 175C*(2017), 8-26. https://doi.org/10.1002/ajmg.c.31552

Martin, A. (2019). An acquired or heritable connective tissue disorder? A review of hypermobile Ehlers Danlos Syndrome. *European Journal of Medical Genetics, 62*(2019), 103672. https://doi.org/10.1016/j.ejmg.2019.103672

Martini, F., Ober, W. C., Nath, J. L., Bartholomew, E. F., & Petti, K. (2018). *Visual anatomy & physiology* (3rd ed.). Pearson.

Nurmatov, U. B., Rhatigan, E., Simons, F. E. R., & Sheikh, A. (2015). $H_1$-antihistimines for primary mast cell activation syndromes: a systematic review. *Allergy 70*(9), 1052-1061. https://doi.org/10.1111/all.12672

Palmer, S., Denner, E., Riglar, M., Scannell, H., Webb, S., & Young, G. (2020). Quantitative measures of tissue mechanics to detect hypermobile Ehlers-Danlos syndrome and hypermobility syndrome disorders: a systematic review. *Clinical Rheumatology, 39*(2020), 715-725. https://doi.org/10.1007/s10067-020-04939-2

Ritelli, M., & Colombi, M. (2020). Molecular Genetics and Pathogenesis of Ehlers-Danlos Syndrome and Related Connective Tissue Disorders. *Genes, 11*(547). https://doi.org/10.3390/genes11050547

Rolfes, M. C., Deyle, D. R., King, K. S., Hand, J. L., Graff, A. H., & Derauf, C. (2019). Fracture incidence in Ehlers-Danlos syndrome – A population-based case-control study. *Child Abuse & Neglect, 91*(2019), 95-101. https://doi.org/10.1016/j.chiabu.2019.03.008

Seniviratne, S. L., Maitland, A., & Afrin, L. (2017). Mast Cell Disorders in Ehlers-Danlos Syndrome. *American Journal of Medical Genetics Part C, 175C*(2017), 226-236. https://doi.org/10.1002/ajmg.c.31555

Shur, N. (2018). A case of broken bones and systems: The threat of irresponsible testimony. *American Journal of Medical Genetics Part A, 179A*(2019), 429-434. https://doi.org/10.1002/ajmg.a.61043

The Ehlers-Danlos Society. (2017, March 9). *'Most neglected disorder in modern medicine'* receives major classification update. The Ehlers-Danlos Society. https://www.ehlers-danlos.com/classification-update/

Thi Dang, M.-T., Ambort, A., & Arrey-Mensah, A. (2019). Recurrent swelling and pain in the abdomen and joints in a patient with hereditary angioedema and Ehlers-Danlos Syndrome. *BMJ Case Reports 12*(2019), e231484. https://doi.org/10.1136/bcr-2019-231484

Tinkle, B. T. (2020). Symptomatic joint hypermobility. *Best Practice & Research Clinical Rheumatology*, Article in Press. https://doi.org/10.1016/j.berh.2020.101508

Tinkle, A., Castori, M., Berglund, B., Cohen, H., Grahame, R., Kazkaz, H., & Levy, H. (2017). Hypermobile Ehlers-Danlos Syndrome (a.k.a. Ehlers-Danlos Syndrome Type III and Ehlers-Danlos Syndrome Hypermobility Type): Clinical Description and Natural History. *American Journal of Medical Genetics Part C, 175C*(2017), 48-69. https://doi.org/10.1002/ajmg.c.31538