An investigation of chronic pain as a much-neglected symptom of Hypermobile Ehlers-Danlos Syndrome

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An investigation of chronic pain as a much-neglected symptom of

Hypermobility Ehlers-Danlos Syndrome

A Review of Literature

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Abstract

Ehlers Danlos Syndrome is a group of heritable loose connective tissue disorders with 13 distinguished subtypes. The hypermobile type of Ehlers Danlos Syndrome (hEDS) is the most common subtype and is caused by a genetic mutation that leads to defective collagen fibrils. This leads to joint instability and hypermobility, skin elasticity, widespread pain, fatigue, and generalized tissue fragility. Chronic pain is reported to be a symptom in as high as 92% of the hEDS population (Voermans et al., 2010); despite this prevalence, there is a significant lack of research, awareness, and treatment standardization regarding pain in hEDS. This literature review aims to investigate the mechanisms of pain hypothesized to be the root of increased pain prevalence in hEDS patients, provide an overview of additional factors that contribute to pain in hEDS, as well as to investigate the efficacies of the therapies which are most often suggested for pain management in these patients. This review covers the three main suggested sources of pain in hEDS: musculoskeletal trauma, central sensitization, and neuropathy. Based on research findings, it is probable that all three of these pain mechanisms play a role in the manifestation of chronic pain in hEDS patients. Fatigue, proprioception and balance deficits, kinesiophobia, depression and anxiety, and deconditioning are additional factors that contribute to the progression of chronic pain. Therapies found to be most successful in hEDS patients in the treatment include targeted physical therapy, myofascial trigger point injections, opioids, ketamine, and medicinal marijuana, with surgery proving to be an effective treatment in limited scenarios. Despite this list of effective treatments, survey studies suggest that those who seek professional treatment present with more complaints of functional impairment in their daily lives than those who do not (Rombaut et al., 2011). This highlights the need for further research.
surrounding effective treatments as well as a standardized treatment guide for physicians treating patients with hEDS.

**Introduction**

Ehlers Danlos Syndrome is a heritable, loose connective tissue disorder that contains 13 subtypes, all sharing variable symptoms which result from abnormalities in the collagen structure (Castori, 2012). The most common of the subtypes is Hypermobility Type (hEDS). The clinical manifestation of hEDS includes joint hypermobility, tissue fragility, widespread pain, fatigue, skin hyperelasticity, and other highly variable symptoms such as gastrointestinal problems and mental illness (Mao and Bristow, 2001). The exact prevalence of this disease in the world population is suspected to be at about 1 in 5,000 people for all subtypes combined, with about 80-90% of these cases being accounted for by hEDS (Tinkle et al., 2017). However, there is very limited research to support this finding as EDS is a highly neglected disease in the medical field, with the lack of education and awareness on behalf of medical professionals playing the main role. Therefore, it is suspected that this incidence is much higher than reported.

Chronic pain has been reported to be a highly variable, yet common, manifestation of hEDS. Although this is a common symptom experienced by hEDS patients, the direct cause(s) of the pain is a part of a continued debate. The most logical reason for chronic pain related to hEDS would be due to injuries resulting from the lack of collagen structure. However, two main theories suggest that there is likely another mechanism that is involved in the development of chronic pain in hEDS patients. The first theory is central sensitization, meaning that the central nervous system is hypersensitive to sensory input. The second theory is neuropathy, which defines nerve damage. In this review of literature, I aim to place my focus on studies that closely
investigate the proposed mechanisms of pain in hEDS patients and provide an overview of emerging therapeutic interventions shown to be successful through clinical studies. The goal of this literature review is to gain a deeper understanding of the origin of pain in hEDS and how to recognize this in patients to work towards a more developed, standardized treatment guide for chronic pain in hEDS in healthcare.

**Disease Background**

**Disease History and Clinical Description**

In the first decade of the 1900s, Edvard Ehlers and Henri Danlos became the first people to document and describe the hypermobility and elasticity of the skin and joints that are most notable in those with EDS (Gensemer et al., 2020). In the year of 1946, "Ehlers-Danlos Syndrome" became the name of this mysterious disease, with the subtypes being distinguished in the late 1960s. These subtypes were documented in the Berlin nosology at this time, with the Villefranche nosology following in 1998. Most recently, EDS was more concisely defined by the EDS International Consortium in 2017 in which 13 subtypes of EDS were classified and of which diagnostic criteria were assigned.

Ehlers Danlos Syndrome Hypermobility Type is hypothesized to be caused by a mutation in one or more genes that is related to collagen structure and integrity. The exact genetic defect related to this subtype is unknown, though there have been suggestions of specific genes in past literature (Castori, 2012). HEDS is thought to be an autosomal dominant heritable disease with a 50% chance of being passed down to children. Although this rate of heritability does not depend on the sex of the child, hEDS tends to have a higher incidence among females. This skewed ratio suggests that the disease is most often transmitted by the mother and may be defined as a genetic
trait with incomplete penetrance (Castori, 2012). This means that despite the trait having the ability to be passed down to male children, they may have a higher chance of being “carriers” of the disease. Thus, there seems to be an increased chance of the female fetus developing the disease in the womb when compared to the male fetus. Additional literature suggests the reason behind this phenomenon to be that females are naturally more flexible and have less muscle tone, leaving them more susceptible to developing this disease to a higher degree of severity (Gensemer et al., 2020). A difference has been noted in past studies in the development of hEDS in boys and girls during puberty (Tinkle and Levy, 2019). In this study, boys and girls scored the same regarding joint hypermobility before going through puberty. Following puberty, the joint hypermobility scores of boys decreased while those of the females increased. This suggests that pubescent hormones play a role in the development of joint laxity. It has also been suggested that females are more often diagnosed with this disorder as they have been noted to be more likely to seek medical attention when it is required than men (Gensemer et al., 2020). Therefore, this incidence of hEDS in females versus males may be skewed for various reasons.

Collagen is found throughout the entire body, including in tendons, joints, fascia, and the skin. Thus, the defective collagen fibrils can cause widespread symptoms that become difficult to manage. The most notable manifestation of hEDS in patients is joint laxity. Joint hypermobility refers to the hypermobility of joints that increases the patient’s susceptibility to soft tissue injury. Joint hypermobility in hEDS most commonly leads to the hyperextension of joints such as the knee and elbow, the subluxation and dislocation of joints, sprains, soft-tissue lesions, increased muscle tension, and widespread musculoskeletal pain (Castori, 2012; Tinkle and Levy, 2019). In addition to joint hypermobility, other typical manifestations of hEDS are skin fragility, organ
prolapse, fatigue, headaches, anxiety, depression, gastrointestinal dysfunction, and kinesiophobia (Castori et al., 2010). The clinical manifestation of hEDS is highly variable from patient to patient, therefore these symptoms should not be generalized for the entire population of hEDS patients.

There are three phases recognized by geneticist Marco Castori in which hEDS naturally progresses (Castori et al., 2010). The first phase is labeled as the hypermobility phase in which the patient can contort their body and perform what is known as “party tricks” using their joint laxity. It is common for these children to partake in sports where their joint hypermobility is celebrated, such as dance or gymnastics. Pain is not common in this phase, though it does have the ability to begin during this period. The second phase is known as the pain phase which begins in the second decade of the patient’s life. Throughout the progression of this phase, the hypermobility of the patient decreases as their joint and muscle pain increases. During this period, the dislocations and subluxations experienced during the first phase may become frequent and debilitating. Finally, the last phase is known as the stiffness phase. This phase is normally entered later in life in one’s 50s or 60s, and chronic pain is often observed in this phase as well. This phase is characterized by the gradual stiffening of joints and a change in the vertebral curvature, and it is noted that anxiety and depression are common.

**Diagnosis**

Genetic testing is available for all subtypes of Ehlers Danlos syndrome except the hypermobility subtype. This is the only subtype that lacks a genetic marker; therefore, its diagnosis must be made purely based on a clinical evaluation. In 2017, the diagnostic criteria were redefined for hEDS by the EDS International Consortium. Since 1998, the diagnostic
criteria have been outlined by the Villefranche nosology, which was done so poorly according to researchers (Tinkle and Levy, 2019). Prior to this refinement, a system known as the Beighton scoring system was the only diagnostic tool used for this disease. The Beighton scoring system was developed in 1973 as a diagnostic tool for generalized joint hypermobility (Tinkle et al., 2017). This scoring system requires five out of nine points to be scored for the diagnosis of EDS to proceed. The system involves the measurement of the hyperextensibility of five different joints. One point is scored for each joint that is considered hypermobile by the system’s standards; these joints include both little fingers, thumbs, knees, elbows, and the trunk (Tinkle and Levy, 2019). This is considered a valuable diagnostic tool as it holds the advantage of being able to be done in-office, it is concise, and it tests a limited number of joints.

Since the redefining of EDS by the EDS International Consortium, the diagnostic criteria for hEDS have become much more specific and rigorous and may require further refining in the future. As outlined by the EDS International Consortium, three criteria must be met by the patient for a clinical diagnosis of hEDS to proceed (Tinkle and Levy, 2019). The first criterion is a positive Beighton score. The second criterion requires that at least two of the three outlined features must be present in the patient. Feature A contains a list of common symptoms seen among those with a generalized connective tissue disorder, and five of these must be present in the patient to meet the criteria. Feature B refers to the presence of a positive family history of hEDS. Feature C requires that at least one of the three listed musculoskeletal complications is present in the patient. Finally, the third criterion requires that three exclusion criteria be met to rule out other diseases.
Misdiagnosis and medical wandering are common issues among hEDS patients, indicating the need for increased awareness and education among medical professionals. Based on feedback from the EDS community, there is a high amount of skepticism present in the medical community regarding the legitimacy of their disease despite its debilitating characteristics (Scheper et al., 2015). HEDS is most often misdiagnosed as fibromyalgia due to the consistent presentation of widespread pain, weakness, and fatigue (Benistan and Martinez, 2019). A survey published in 2010 reported that out of 16 major rare diseases, EDS had the longest diagnostic delay (Castori et al., 2010). This same survey reported that patients with EDS consulted with up to 20 specialists before finally receiving an accurate diagnosis. This is a major issue for those affected by this disease as this may have detrimental effects on the quality of life of the patient. A delayed diagnosis results in wasted time and money, leaving the patients vulnerable to wrong therapies, the worsening of the disease and mental state, and excessive expenses. Therefore, further research on this disease must be published in order to increase awareness among medical professionals to ensure that a proper and timely diagnosis is possible for all EDS patients.

Joints tested in the Beighton scoring system (Tinkle and Levy, 2019).
Treatment

As of today, there are no official guidelines regarding the treatment of hEDS. Therefore, treatment plans for hEDS patients typically involve the management of individual symptoms to improve the quality of life of patients through interventions such as medication and physical therapy (Gensemer et al., 2020). Physical therapy is considered to be the most crucial of the suggested therapeutic interventions as the physical therapist is capable of creating a highly specific treatment plan and implementing manual therapy (Reychler et al., 2021). Because Ehlers Danlos Syndrome-Hypermobility Type is such a variable disease that manifests itself differently in every patient, its treatment should be highly individualized for each patient with the focus being to minimize the burden of each symptom experienced.

Chronic Pain in hEDS

Prevalence

As defined by Merriam Webster’s medical dictionary (2021), pain is a bodily sensation that is the result of naked nerve endings transmitting the signal related to the painful signal tied to tissue damage to the spinal cord, resulting in physical discomfort. When chronic, pain can be debilitating and has a major negative effect on the quality of life of a person. Although chronic pain has been documented to be the most frequent manifestation of hEDS, it remains a highly neglected symptom of hEDS by medical professionals (Kalisch et al., 2019). According to this same source, misdiagnosis of fibromyalgia is frequent among these patients with a documented rate of about 42%. Kalisch et al. (2019) report that joint and muscle pain prevalence among hEDS patients reaches up to 90-100%. Despite this high incidence of chronic pain among hEDS patients, there is a lack of standardized recognition and treatment of pain following a diagnosis.
of this disease. Pain symptoms and their severity have often been reported by these patients to be underestimated or dismissed entirely by physicians (Benistan and Martinez, 2019). The opioid epidemic has also certainly affected the treatment of pain patients, leading to the increase of disbelief among physicians towards patients seeking pain management. This problem only highlights the need for further pain research regarding hEDS and a standardized guideline for pain management specific to this disease.

Source of Pain in hEDS

Due to the lack of research in this field, the exact mechanism behind chronic pain in hEDS is a topic of ongoing debate. Several factors influence the severity, location, and type of pain that is experienced by the hEDS patient. However, the main factors that will be covered in this paper are biomechanical, neurological, psychosocial, and factors of physical fitness. These factors have been reported in literature to be the major determinants of chronic pain in hEDS (Scheper et al., 2015). The reason and physiology behind the neurological component of the chronic pain experienced in hEDS have yet to be agreed upon as a research community; however, there are promising studies that have been published in recent years that indicate that a more consistent explanation regarding the pain pathology of this disease will be available in the near future. This would allow clinicians to better recognize chronic pain in hEDS and allow them to create a better treatment plan based on their educated distinction of the type of pain being experienced.
Biomechanical Factors Influencing Pain in hEDS

Joint Instability and Musculoskeletal Trauma

Joint instability is the most common and widely recognized manifestation of Hypermobile-Ehlers Danlos Syndrome. This joint instability, as previously described, is caused by a presumed genetic mutation that causes defective collagen to be present in the body (Tinkle et al., 2017). Collagen is found in many areas of the body that are involved in maintaining the structure of the musculoskeletal system. This defective collagen then leads to the reduced stability of joints, ligaments, and tendons. When there is a deficit of structural integrity in the body, this increases the risk of injury and also requires an unnatural compensation mechanism to be put into place to restore stability, causing a number of negative musculoskeletal consequences (Scheper et al., 2015).

There are two broad types of pain regarding the nervous system: the first is nociceptive, which means that pain pathways are being activated at a higher rate than normal. The one seemingly obvious source of heightened nociceptive activity would be musculoskeletal trauma. Hyperelasticity in hEDS leaves patients vulnerable to soft tissue damage (Voermans et al., 2010) and leads to microtraumas on joint surfaces (Scheper et al., 2015). These microtraumas result in an increase in nociceptive activity as expected, which then leads the patient to compensate for the painful joint. This compensation may be conscious or subconscious. Subconscious compensation involves the muscles straining to maintain stability amidst the loss of joint function. Conscious compensation involves adjusting certain movements or postures to relieve pressure placed on the damaged joint, which places a more intense load on these other areas of the musculoskeletal system. These compensation mechanisms place additional strain on the
musculoskeletal system and intensify the nociceptive activities of the nervous system that are already heightened due to the injured joint. Although this is a simple answer to a complex question, the way that pain manifests itself in hEDS patients cannot be explained by this mechanism alone.

Hypermobile joints in patients with hEDS (Castori et al., 2012).

**Proprioception and Balance**

Decreased proprioception has been noted within the hEDS community. Proprioception is defined as the ability to understand where your body is in space (Merriam-Webster, 2021). In the early stages of disease progression, poor balance and proprioception may be noted, with patients being described as “clumsy” in children and even adults. Poor balance and decreased reflexes in the knee extensors have been documented in hEDS patients and are linked to decreased activity levels (Engelbert et al., 2017). According to this same source, decreased joint proprioception has a major influence on the association between muscle strength and activity limitations. Reduced proprioceptive acuity leaves the patient more vulnerable to injury as it heightens their chances of making movements that are beyond what they intended on performing, ultimately increasing
pain levels (Scheper et al., 2015). Proprioceptors in the joints are thought to be damaged in hEDS patients as a direct result of the joint hypermobility, damaging and stretching the nerves beyond their limits (Engelbert, 2017). Balance, proprioception, and reflexes are extremely important for safe and painless mobility, and their deficits in hEDS patients contribute to increased musculoskeletal pain and atrophy as well as activity limitations among these individuals.

**Neurological Factors**

**Central Sensitization**

A mechanism of pain that has been hypothesized to be the root of chronic pain symptoms in hEDS is known as central sensitization. This refers to the overactivity of nociceptive pathways within the patient’s central nervous system. One study performed by Kawasaki et al. (2008) showed that pro-inflammatory cytokines (PICs) contribute to sensitization. These are proteins that are responsible for the upregulation of inflammatory responses in the body. It has been hypothesized from previous studies that PICs are induced in glial cells following injury to the nerves and subsequent inflammation. As we know, injury and microtraumas are common with this disease, therefore there is likely to be higher PIC activity in hEDS individuals than in healthy individuals. Following their induction, this study suggests that the PICs work to suppress inhibitory neurotransmission and enhance excitatory neurotransmission. The suppression of inhibitory neurotransmission is known as disinhibition. The PICs mentioned in the article were found to be responsible for the transcription of the protein CREB, which may be the main contributor to long-lasting pain sensitivity. This hypothesis is supported by the findings of Leone et al. (2020) in which the participants of their study were found to have a reduction in
endogenous pain inhibitory control, also known as disinhibition. This signifies that participants felt a more intense pain following a “conditioning” stimulus, rather than feeling less intense pain. This inability to control nociceptive input following repeated stimuli is hypothesized to lead to central sensitization.

In a study published in 2016 (Di Stefano et al.), it was found that central sensitization may very well be a component of the chronic pain that those with hEDS experience. This study used quantitative sensory testing to measure pain severity in various areas of the body which showed that hEDS sufferers experience chronic, widespread pain similarly to those with fibromyalgia. The study participants also experienced hyperalgesia to hot and cold stimuli as well as an increased wind-up ratio. A wind-up ratio regarding pain is defined as an increased pain response after undergoing a repeated painful stimulus (Di Stefano et al., 2016). This finding is supported by that of Benistan and Martinez (2019) in which an increased wind-up ratio was present in 37% of patients following the application of heat and cold stimulus on painful joints. These two results from the 2016 study are major indicators of central sensitization as the main mechanism in hEDS pain.

Di Stefano et al. (2016) argue that the diagnosis for neuropathic pain requires an indication that the somatosensory nervous system has undergone some form of damage, and that this study did not prove this to be true in hEDS patients. This study utilized a questionnaire that is a very specific survey for neuropathic pain, known as the DN4 survey. Along with this questionnaire, objective tests that tested somatosensory nerve damage included a motor and sensory nerve conduction study involving superficial electrodes placed along major nerves in the body. Laser-evoked potentials were also studied in participants using laser beams to elicit
pin-prick sensations to the participant’s hands and feet to determine the lowest threshold at which they could perceive 50 percent of the stimuli. Despite the conclusions from prior studies, the participant responses to the DN4 questionnaire indicated that neuropathic pain was not the cause of the widespread pain experienced by EDS patients. The nerve conduction study also failed to support the hypothesis that there is somatic sensory nerve damage present in Ehlers Danlos Syndrome patients. The authors believe that the reason for the discrepancy in results is due to variation in the methods used to diagnose neuropathic pain.

The results of this study that support the hypothesis of central sensitization as the main mechanism behind the pain experienced by EDS sufferers include the heat and cold stimuli threshold and wind-up ratio results. These results demonstrate that the participants had a heightened pain sensitivity to heat and cold and that the pain lasted for a longer period after the stimulus was removed when compared to healthy participants. The other result that indicates that central sensitization plays a role in chronic pain is the reported widespread pain experienced by patients. This symptom was reported through the completion of the fibromyalgia rapid screening tool. The authors hypothesize that the chronic pain experienced by EDS patients has an underlying mechanism like that of fibromyalgia. According to the authors, these are all major indications that central sensitization is the main underlying mechanism in chronic pain among hEDS patients and that neuropathy is not present among these patients.
Examples of pain diagrams from the study by Di Stefano et al. (2016).

A separate study published in 2014 by Rombaut et al. presents subsequent data to support the hypothesis that central sensitization plays a role in chronic pain in hEDS, in addition to neuropathic pain. In this study, 23 females with hEDS underwent an assessment to measure pain pressure thresholds. The participants of this study tested with pain thresholds that were significantly lower than those of the healthy control group. The pain pressure thresholds were tested on various areas of the body, and all areas, excluding the right calf, resulted in a lower threshold for hEDS participants. The pain thresholds also proved to be lower even at asymptomatic areas of the body. The participants were also asked to fill out a pain diagram along with a questionnaire designed to test for neuropathic pain, known as the Pain Vigilance and Awareness Questionnaire. The questionnaire provided split results, indicating that about half of the participants suffer from mainly neuropathic pain, and the other half suffer from mainly nociceptive pain due to central sensitization. The pain diagrams submitted by the participants showed a significant difference in the amount of pain felt on the body between the control and hEDS groups. The diagrams of the hEDS participants covered a mean of 31% of the body.
surface, while the diagrams of the healthy controls covered a mean of 1% of the body surface. This widespread pain felt by hEDS participants, along with the lowered pain thresholds even at asymptomatic sites, allowed the authors to conclude that central sensitization plays a role in chronic pain in this disease.

**Neuropathic Pain**

An additional hypothesis that aims to explain the underlying mechanism of pain in hEDS patients is neuropathy, which is the second type of broad pain regarding the nervous system. Neuropathic pain is caused by damaged nerves that are responsible for transmitting information from your peripheral to your central nervous system (Merriam-Webster, 2021). According to Castori and Voermans (2014), it is thought that the frequent dislocations, subluxations, and general joint laxity places abnormal pressure on peripheral nerves, leading to their damage. It is hypothesized by Kawasaki et al. (2008) that damaged nerves create an imbalance between the inhibitory and excitatory synaptic actions within the dorsal horn neurons in the spinal cord. This, in turn, is thought to cause neuropathic pain by enhancing excitatory synaptic transmission while also inhibiting inhibitory synaptic transmission, known as disinhibition. As a result, nociceptive pathways are enhanced through excitation without inhibitory control. This has been explained in research to be the cause of central sensitization as well, so it is likely that these two forms of pain are not mutually exclusive. As mentioned previously, Di Stefano et al. (2016) did not find evidence for the presence of neuropathy in hEDS patients. However, several other researchers have published articles that contradict these findings.

It has often been found in studies researching neuropathic pain incidence in hEDS patients that approximately half of the participants are likely to suffer from neuropathic pain.
based on validated surveys for diagnosing neuropathic pain (Rombaut, 2014; Camerota, 2011). Although these surveys are deemed to be a highly specific tool for this diagnosis, additional methods have since been utilized to make this determination.

A study supporting the presence of neuropathic pain in hEDS patients came to this conclusion by obtaining skin biopsies from the participants (Cazzato et al., 2016). 100% of these skin biopsies showed a significant decrease in intraepidermal nerve fiber density. This means that the nerve fibers found within the epidermis in hEDS patients were found to be less dense in the skin than in control patients. This indicates the degeneration of the nerve fibers, which is, therefore, an indication of small fiber neuropathy. To support this finding, 95% of these participants were indicated to have neuropathic pain according to the DN4 questionnaire. It is unknown whether or not the loss in the density of these nerve fibers is directly related to the cause of neuropathic pain or is simply a marker of small fiber neuropathy.

Benistan and Martinez et al. (2019) completed a study in which they researched the source of pain in hEDS patients using vibratory and quantitative sensory testing, as well as surveying. This study not only proves that neuropathic pain is present in hEDS patients using the DN4 questionnaire but also suggests the incidence of neuropathic pain as a result of the quantitative sensory testing. The sensory testing used in the study involved the application of heat and cold stimuli to determine pain thresholds. Hypoesthesia, or the loss of feeling, was found in participants following heat stimulus. This finding is suggestive of small fiber neuropathy in these participants. Additionally, the DN4 questionnaire found that 75% of participants suffered from neuropathic pain. From these results, we can assume that small fiber
neuropathy does play a role in the development of chronic pain in hEDS patients with neuropathic pain being present in such a majority of the samples.

Psychosocial Factors

Depression and Anxiety

Psychological conditions among hEDS patients are all but rare. The most common conditions are anxiety and depression and are most frequent in the late-second and third stages of the disease (Castori et al., 2010). In one retrospective study completed by Hershenfeld et al. (2015), 42.5% of a sample of patients with classic and hypermobility type EDS patients were found to suffer from a psychiatric condition, with 22% of these patients suffering from more than one condition. This is a much higher rate than what is found among the normal population, which is estimated by the National Institute of Mental Health to be about one in five adults in the United States (2020). This is suggested to reflect the decreased quality of life that results from the comorbidities of hEDS and their contribution to the decline of hEDS patients in the later stages of the disease (Baeza-Velasco et al., 2018).

Graph depicting the higher prevalence of psychiatric disorders among hEDS patients (Hershenfeld et al., 2015).
Fatigue

Fatigue is an extremely common complaint among the hEDS community, taking place as the most common neurologic complaint alongside chronic pain (Castori, 2012). Much like chronic pain, fatigue is very poorly characterized within the scope of this disease as its pathology remains largely unknown (Cetelli et al., 2021). This symptom usually coincides with the increase in pain levels in the second phase of the disease. The diagnosis of chronic fatigue is also commonplace among hEDS patients (Tinkle et al., 2017). Fatigue is considered to be chronic when it lasts longer than six months consistently. In a study conducted by Voermans et al. (2010), 31% of the functional impairment reported by hEDS patients was caused by pain and fatigue together, with fatigue being the leading cause of impairment between the two. Fatigue most certainly contributes to the overall decline and pain chronicity of hEDS patients through their disease progression but remains another neglected symptom of the disease.

Kinesiophobia

Kinesiophobia has been found to affect a large portion of those affected by hEDS and is a direct result of the pain and fatigue associated with this disease. Kinesiophobia is defined as the fear of movement or reinjury (Celleti et al., 2021). Chronic fatigue is a common comorbidity of chronic pain in hEDS; this level of fatigue can be highly debilitating and is suggested to play a role in the decline of hEDS patients throughout the second phase of the disease. It is controversial whether fatigue plays a causal role in the eventual mental and physical decline of hEDS patients or if it is a symptom that is a result of the patient's decline (Hershenfeld et al., 2015); regardless, fatigue is considered to be a crucial factor in the development of kinesiophobia (Scheper et al., 2015).
In one study published by Celleti et al. (2021), 93% of patients surveyed scored at a level that was highly suggestive of the presence of kinesiophobia. It was found in this study that there is a correlation between the presence of pain and kinesiophobia, but not the severity of pain. Instead, the severity of fatigue was found to have a significant correlation with kinesiophobia in hEDS patients. These findings suggest that kinesiophobia is more directly related to the coping mechanisms of the patient based on their fatigue and the presence of pain rather than the severity of the pain itself.

Factors of Physical Fitness

Deconditioning

Scheper et al. (2015) describe the effects of kinesiophobia as a cycle rather than just another symptom of hEDS. In the case that the patient experiences a new pain, this newfound fear of this pain will lead to the avoidance of the contracting of the related muscles. This, in turn, leads to muscle performance which is less than what is considered maximal contraction for that person. As described previously, muscle performance is vital to maintaining joint stability in those with joint hypermobility through the compensation mechanisms it provides. With decreased muscle tone, these compensation mechanisms are not as effective, leaving the patient more vulnerable to injury, which then results in more pain.

This loss of muscle tone is known as deconditioning (Baeza-Velasco et al., 2018). Deconditioning may not only lead to an increased perception of pain, but also an increased level of mental and physical fatigue (Tinkle and Levy, 2017). Deconditioning of the musculature of the patient leaves the individual more vulnerable to injury, worsening of mental illness, and
increased intensity of kinesiophobia. This cycle can be crippling and once it has advanced, it is very difficult to escape from.

Cardiovascular Function

One direct result of deconditioning is reduced cardiovascular functioning. This is hypothesized to contribute to the orthostatic intolerance that appears to be prevalent among hEDS patients (Hershenfeld et al., 2015). Orthostatic intolerance refers to the inability to maintain stable blood pressure when changing from a seated or lying position to an upright or standing position. According to Kalisch et al. (2019), pain is aggravated as a direct result of the decrease in cardiovascular functioning, known as cardiovascular dysautonomia. Cardiovascular dysautonomia is known to increase fatigue as well, contributing to the vicious cycle of deconditioning, kinesiophobia, and pain. In order to penetrate and halt this cycle, action must be taken early in its making. Early therapeutic intervention is crucial to maintaining muscle tone.

A depiction of the chronic pain cycle (Scheper et al., 2015).
and cardiovascular function in the patient, allowing for the maximal quality of life to be accomplished.

**Therapeutic Interventions**

As discussed in the introduction to this paper, there is no formal guideline for pain management or therapy for hEDS patients. In the absence of official treatment guidelines, it is encouraged that hEDS patients receive highly individualized treatment plans intending to minimize the burden of each symptom. HEDS manifests itself very differently in each patient, therefore it is difficult for researchers to generalize a treatment plan for all affected individuals. However, there are suggestions of various treatments supported by studies published by researchers that have shown to ameliorate major symptoms shared among the majority of hEDS patients. Although it is impossible to cover every single type of therapy available, therapies stemming from three broad categories will be discussed: physical therapy, medicinal therapy, and surgical intervention. These are the therapies that are most commonly used for the treatment of hEDS patients and have been seen to have the most success in improving the quality of life of these individuals.

**Physical Therapy**

The most common form of therapy that is prescribed for hEDS patients is physical therapy. It is also thought to be the most effective form of therapy for this population, though there is a lack of research evidence to compare various treatment efficacies for this patient group. In a study conducted by Demes et al. (2020), 60.6% of participants rated their experience in physical therapy as moderately to extremely helpful, with 89% of the entire study group having participated in physical therapy at some point before the study.
As described in the overview of the disease, hEDS patients suffer from a wide variety of debilitating symptoms that make it very difficult to maintain muscle tone and therefore maintain joint stability. There are two very common physiotherapy paths that therapists normally follow when treating hEDS patients: a general physical therapy program aimed at increasing overall muscle strength, and a targeted program aimed to correct the motion control of the affected joints. A study performed by Kemp et al. (2009) compared the two routes of physical therapy for children suffering from joint hypermobility symptoms in regard to their effectiveness in reducing pain. The study found that targeted physiotherapy appeared to be the most beneficial overall. However, the children assessed for this study all experienced significant improvements in their pain scores, regardless of the form of physical therapy that was administered over time.

The general physical therapy program that was administered for this study involved a set of exercises that were geared towards increasing overall fitness and muscle strength. These exercises included squat thrusts, sitting-to-standing, jumping jacks, and shuttle runs. As the study progressed, new exercises were added, and the difficulties were increased. The targeted physiotherapy program administered for this study aimed to increase the functional stability of the symptomatic joints by retraining the muscles involved in motion control. The steps involved in this form of physiotherapy include identifying the neutral resting position of the symptomatic joint, maintaining these postural muscles while moving an adjacent joint and while active, and muscle stretching. Through these steps, it is the goal to instill these postural corrections in the patient’s muscle memory using proprioceptive techniques. The results of this study indicate that both forms of physiotherapy are effective forms of treatment in hEDS patients, with targeted physiotherapy suggested to be more effective in reducing pain scores.
A separate study completed by Celleti et al. (2021) took this approach to physiotherapy even further, labeling it as a neurocognitive form of therapy. This form of therapy involved guided felt sense, which is a process by which the participant “rewired” the way that they perceived their pain. The goal of this form of therapy was to better learn how to control the elements of their daily movement as well as enhance and alter their perception of pain to gain a better understanding of their pain and its source. The results of this study showed very significant improvement in the participants’ pain, fatigue, disability associated with pain, and kinesiophobia.

Another study performed by Ferrell et al. (2004) focused on the proprioceptive aspects of physical therapy by aiming to increase the stimulation of Ruffini nerve endings. These nerve
endings are known to be slow-adapting and contribute to proprioception (Merriam-Webster, 2021). The exercises in this study were designed to specifically stimulate these nerve endings in the knee joint, which involved repeated pressure on the symptomatic joint via closed-kinetic chain exercises. These are exercises that you may do standing in one position, including squats, planks, etc. These exercises were chosen as they not only improve proprioception but also place less strain on the joints and focus on recruiting multiple muscles to contract at once, overall improving joint stability. The participants in this study experienced a significant improvement in muscle tone, proprioception, balance, and pain scales.

Physical therapy tends to be the first choice for therapeutic intervention, and for good reason. Joint instability is often met with muscle tension to compensate for the laxity. Muscle tone must be maintained to prevent deconditioning, which allows comorbidities such as chronic fatigue and depression to have an increased influence on the patient’s quality of life. Physical therapy also allows for a highly specific treatment plan to be created with manual therapy being implemented when necessary (Reychler et al., 2021). Although physical therapy is an excellent option for treatment for hEDS, this may not always be enough to lessen the burden of all the symptoms of this disease for some patients. In this case, procedural intervention may be required.

Procedural Interventions

Procedural intervention refers to any type of intervention that requires a specific procedure performed by a physician. One procedural intervention that has been shown to be effective in hEDS patients suffering from musculoskeletal pain is myofascial trigger point injections. The myofascia is known as the soft tissue that surrounds the muscle. If there is stress
or damage done to the muscle, such as excessive muscle tension as a result of joint laxity, trigger points, also known as knots, develop and become painful (Tewari et al., 2016; Castori et al., 2015). These painful myofascial trigger points may be treated with trigger point injections, which are typically a combination of a local anesthetic, saline, and/or a corticosteroid (Hammi et al., 2021). In one case study conducted by Tewari et al. (2016), a 30-year-old female with hEDS presented with chronic back pain and was administered two trigger point injections. Instructions to administer heat therapy, massage, stretches, and NSAIDs for a week following the injections were given by the physician. This patient reported 60-80% pain relief after one week following treatment. By the end of the second week, the pain had reduced by half of the prior week’s pain score. The patient reported being mostly pain-free for the following eight months.

The physiology of myofascial trigger points is not well understood, yet they are reported to occur in 30-93% of all people suffering from pain (Tewari et al., 2016). This treatment is a relatively non-invasive, simple procedure that is suggestive of long-lasting results when combined with physical therapy. HEDS patients are vulnerable to myofascial trigger points as their compensation mechanism for their joint laxity is increased muscle tension to induce stability. Thus, the use of myofascial trigger point injections in hEDS patients suffering from chronic musculoskeletal pain would likely prove to be effective in reducing pain in the patient while holding the advantage of avoiding an invasive or time-consuming procedure.

Another common procedural intervention considered for the treatment of hEDS is surgery. Surgery is often thought to be a “quick fix” for musculoskeletal issues by some; however, due to the slowed wound healing and joint laxity that is seen in hEDS, surgical intervention often worsens the patient’s quality of life in many ways (Gensemer et al., 2020). In
one study conducted by Rombaut et al. (2011), survey results showed that patients with hEDS who did receive surgical treatment at some point in time had a higher level of functional impairment than those who did not. Despite this finding, 70.9% of patients in the study had undergone surgical treatment, with most being completed on a major joint such as the knee, shoulder, etc. Only 33.9% of these patients reported that the surgical intervention was successful, indicating that it had a positive effect on their symptoms. Therefore, surgical intervention must be considered with caution when treating an hEDS patient as it is suggestive of being a “last resort” method of treatment for this population. If it is decided to be utilized as a method of pain relief, extra precautions are suggested to be taken, such as gentle force during dissection, minimal tension used for suturing, and the use of steri-strips and additional layers of sutures to avoid the reopening of the wound (Tinkle et al., 2017).

**Medicine**

In a survey conducted by Demes et al. (2020), the therapies used by hEDS patients were recorded as well as their feedback about each therapy. The medicinal therapies found to be most efficacious according to the patients were opioids and various forms of marijuana. In this study, opioids were reported to be moderately to extremely helpful in 88.1% of the patients who used them as a treatment for their chronic pain. Opioids have been reported to be the most effective at higher pain levels than at lower pain levels in hEDS patients, where NSAIDs have been reported to be more efficacious. In this same study conducted by Demes et al. (2020), opioids were being used as pain management among 70% of the study cohort. The rate of opioid usage, according to this same source, is suspected to be at about 34% for the general population. Despite this increase in opioid usage in hEDS patients, a study conducted by Rombaut et al. (2011) reported
that patients who used opioids for pain management had a significantly higher number of complaints of functional impairment than those who did not. This result indicates that those using opioid medication to treat their pain related to hEDS experienced a higher level of dysfunction in their lives. Thus, opioid medication may be effective at treating a high degree of pain, but it may come at the cost of functional impairment in hEDS patients as well as a slew of unwanted side effects and a high risk of addiction with long-term use.

The second medicinal therapy that was suggested to be the most effective according to a survey of hEDS patients is different forms of marijuana (Demes et al., 2020). These forms of marijuana, rated least effective to most effective, included marijuana concentrate, topical marijuana, edible marijuana, vaporized marijuana, marijuana tinctures, and smoking marijuana, with the last two forms having the same self-reported efficacies. It was reported that marijuana was used when experiencing higher pain levels, which may indicate a preference for marijuana use with more severe chronic pain. Marijuana preference among this population may be explained by the simultaneous management of anxiety that this treatment option offers, as anxiety surrounding pain is prevalent in hEDS patients.

A case report of an 18-year-old female with hEDS is consistent with these findings as well as prior research surrounding chronic pain and marijuana use (Dar, 2021). This patient experienced chronic pain as a result of an unsuccessful surgery aimed to treat her TMJ dysfunction. Physical therapy and opioid use were minimally successful in reducing her pain, leading her to self-administer vaporized marijuana. Within three months of beginning self-administration of marijuana, she was able to cease all opioid consumption as well as dramatically decrease the amount of inpatient and emergency care required. This treatment was
used alongside continued physical therapy and proved to be highly transformative in this patient’s case. Marijuana use in hEDS patients is considered to be an effective method of treating chronic pain with improvements in pain levels and quality of sleep (Jensen et al., 2015). However, this form of treatment does come with potential side effects. These may include decreased neuropsychological functioning, decreased alertness, drowsiness, as well as concerns for its possible effects on brain development. Thus, care must be taken when choosing the proper treatment for each individual.

One last medication that has been found to reduce pain scores among hEDS patients is ketamine. This medication is an analgesic medication commonly used in place of opioids in pain management as well as for general anesthesia. In one case study, ketamine was found to be effective in reducing an hEDS patient's chronic pain while allowing her to decrease the amount of opioid medication being consumed, ultimately increasing the quality of life of the patient (Lo et al., 2016). Ketamine has been found to be effective in treating neuropathic pain as well as pain due to central sensitization. The mechanism behind ketamine as a pain relief drug is unclear, though it is hypothesized that it restores the balance between pain inhibition and facilitation. This balance is thought to be disrupted in both neuropathic pain as well as central sensitization, known as disinhibition (Kemp et al., 2009), thus this hypothesis would be consistent with prior explanations for pain mechanisms in hEDS.

According to Rombaut et al. (2011), survey participants with hEDS who have received treatment including surgery, medication, and physical therapy are more functionally impaired and present with more complaints of pain than those who have not received these forms of treatment. This finding indicates the need for a new and more standardized therapeutic approach
to the clinical treatment of hEDS as well as further research to investigate which therapies prove to be most effective in this specific population.

**Conclusion**

Hypermobile Ehlers Danlos Syndrome (hEDS) is a rare, heritable connective tissue disorder that causes joint instability, chronic pain, fatigue, tissue fragility, and other variable symptoms. Despite being reported frequently as a symptom of hEDS, chronic pain is a highly neglected symptom of hEDS as there are no standardized treatment guidelines for physicians to follow when treating patients. There is a complete lack of education and awareness of this disease among the healthcare profession and research community alike. The lack of research, genetic testing, and education tools available for hEDS makes it incredibly difficult for patients to seek proper care from specialists. As discussed in this review, there is a major diagnostic delay for hEDS patients, which lessens the quality of life of these individuals significantly. This effect is seen on an even larger scale when patients seek treatment for chronic pain associated with their disease, which is often already underestimated in more recognized diseases. Chronic pain in hEDS is highly under-researched, thus the underlying mechanism of the pain is a topic of debate.

The three hypotheses suggested by researchers to explain the underlying mechanism of chronic pain in hEDS include musculoskeletal trauma, central sensitization, and small fiber neuropathy. The research that has been covered in this paper serves as overwhelming evidence that all suggested mechanisms of pain play a role in the development of chronic pain. The first pain mechanism of musculoskeletal trauma may be the most obvious. The deficit in structural integrity resulting from the defective collagen leads to a higher risk of injuries, dislocations, and subluxations, as well as microtraumas. These injuries then lead to a higher nociceptive activity.
Central sensitization also leads to higher nociceptive activity as a result of recurring injuries, sensitizing the central nervous system to nociceptive input. Results of participant studies, including participants presenting with an increased wind-up ratio, a lower pain/pressure threshold even in asymptomatic areas, and widespread pain. Finally, small fiber neuropathy is thought to be present in hEDS due to hyperelasticity and has been proven by skin biopsies, neuropathy questionnaires, hypoesthesia following heat stimulus. Both central sensitization and neuropathic pain are thought to be propagated by increased upregulation and disinhibition in the central nervous systems of hEDS patients. This mechanism can be supported by research that found that the central nervous systems of hEDS participants were unable to properly respond to a painful, repeated “conditioning” stimulus by lowering the perceived pain intensity; instead, the participant perceived the same amount of pain throughout. Since this mechanism is involved in the propagation in both pain pathologies, they likely coexist in the central nervous systems of hEDS patients just as studies suggest.

The therapies found to be most efficacious based on clinical and self-reported research include target physical therapy programs, myofascial trigger point injections, opioids, marijuana, and ketamine. Surgery is also commonly suggested for the treatment of this disorder but is beneficial in limited circumstances. Physical therapy is apparent to be the most helpful of all available treatments as it was found in several studies to decrease the pain scores of participants dramatically, and it offers the benefit of a highly individualized treatment program. Myofascial trigger point injections have limited research to support their efficacy, though it appears in literature to be a non-invasive, simple, and long-lasting treatment. More research must be
conducted regarding effective pain medication for hEDS as much of the data regarding their efficacy is self-reported and their side effects were not often considered in the literature.

Although there is literature that offers explanations for the debilitating chronic pain experienced by hEDS patients, there is still much research to be done to determine the pain pathology of hEDS as fact. If there is more than one pain mechanism at hand as the literature suggests, then pain management must be based on the overruling mechanism present in the patient. A standardized protocol for the recognition, diagnosis, and treatment of hEDS must be created, as well as educative tools, such as brochures, for both patients and physicians to be available in the clinical setting. There is also a need for more research to be done to investigate new and effective treatment plans for pain management in hEDS. In the past two decades, the research and medical community have given much more recognition to this complex and rare group of heritable disorders. However, there is still much work to be done to raise awareness for this disease as the diagnostic delay remains high and the quality of life low. A change in the diagnosis and treatment of hEDS patients will not be easy, though it is possible with the proper education and research available to the community and healthcare providers alike.
References


