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# Comprehensive Overview of Ehlers-Danlos Syndrome: Diagnosis, Management, and Unmet Needs

**[1]Pritam Singha, [2]Md. Asif Iquebal**

[1]Department of Pharmacy Practice, Parul Institute of Pharmacy, Parul University, Vadodara, Gujarat, India, 391760

[2] Calcutta institute of pharmaceutical technology and AHS Maulana Abul Kalam Azad University of technology.

**Corresponding address:**

Pritam Singha,

**Abstract**

Ehlers-Danlos syndrome (EDS) comprises a group of inherited connective tissue disorders characterized by defects in collagen synthesis or processing, affecting skin, joints, and internal organs. With 13 recognized subtypes, EDS presents a broad spectrum of clinical manifestations including hypermobile joints, skin hyperextensibility, and fragile connective tissues. The prevalence of EDS is estimated between 1 in 5,000 and 1 in 10,000 individuals, with specific subtypes varying in rarity and clinical features. Diagnosis relies on clinical evaluation, including skin and joint assessments, as well as genetic testing when applicable. Management focuses on symptom relief and supportive care, encompassing physiotherapy, pain management, and addressing joint stability. Despite advances in classification, many patients encounter challenges in obtaining accurate diagnoses and effective treatments due to limited specialist availability and awareness. Research is ongoing to better understand the genetic and molecular underpinnings of EDS and to develop targeted therapies. Multidisciplinary care, involving specialists across various fields, is essential for optimizing patient outcomes and addressing the comprehensive needs of individuals with EDS.

Keywords: Ehlers Danlos Syndrome, Connective tissue disorders, skin hyperextensibility, joint stability, hypermobile joints

## Introduction

Ehlers-Danlos syndrome encompasses a collection of diseases that impact connective tissues, which provide support to the skin, bones, blood vessels, and various other organs and tissues. Abnormalities in these connective tissues lead to a variety of signs and symptoms, varying from mildly hypermobile joints to potentially serious health issues [1].

It is primarily identified by a range of clinical signs, which include the potential to stretch the skin excessively, slow healing of wounds that often result in thin, wrinkled scars, and increased joint mobility. Individuals with this condition may also experience a tendency to bruise easily and exhibit overall fragility of connective tissues throughout the body [2].

Occasional and typical connective tissue diseases encompass a wide array of conditions and syndromes, including hereditary disorders like ED syndromes and related conditions, as well as uncommon systemic immune-related diseases such as recurrent polychondritis, systemic sclerosis, mixed connective tissue disease, inflammatory idiopathic myopathies, and antiphospholipid syndrome [3]. This weakness can manifest as skin that is prone to tearing and scarring, vascular weakness leading to easy bruising, and a variable tendency to bleed, along with other signs of generalized soft connective tissue fragility [4].

Most forms of this disease are identified by an unusually wide range of joint movement, known as hypermobility, which is particularly prominent in the hypermobile type. Infants and children those who are having this hypermobility, they can face difficulties to develop motor skills such as sitting, standing, and walking [5]. The instability of their loose joints makes them susceptible to dislocations and chronic pain.

Individuals with ED syndromes frequently exhibit a soft, velvety skin texture that is highly stretchable and prone to tearing. Easy bruising is a common symptom across most forms of the disorder. Certain subtypes can lead to abnormal scarring, such as the classical type where wounds split open with minimal bleeding and develop into widened, distinctive "cigarette paper" scars over time [6-8].

It consists of a collection of inherited disorders affecting connective tissues, are often associated with musculoskeletal, dermatological, and cardiovascular issues. Historically classified into over ten types, EDS was restructured into 13 distinct types in 2017 based on their symptomatic characteristics [9,10]. These types include Classical (cEDS), Classical-like (clEDS), Cardiovascular (cvEDS), Vascular (vEDS), Hypermobile (hEDS), Arthrochalasia (aEDS), Dermatosparaxis (dEDS), Kyphoscoliotic (kEDS), Brittle Cornea Syndrome (BCS), Spondylodysplastic (spEDS), Musculocontractural (mcEDS), Myopathic (mEDS), and Periodontal (pEDS). The overall prevalence of EDS is estimated at 1 in 5,000, with multiple causative genes identified for each type, although some remain unknown.

## Background

The overall prevalence of ED syndrome is approximately to be between 1 in 5,000 and 1 in 10,000 individuals. However, the epidemiology of the particular EDS subtypes is broadly unknown. EDS can be noticed worldwide, which affects both males and females with no racial predisposition. The 13 recognized EDS variants are clinically and genetically heterogeneous, which results due to the defects in the synthesis or structure of fibrillar collagen [11,12].

Connective tissue cells produce a fibrous protein named collagen and it serves as a key component of skin and bone. As the most prevalent protein in mammals, it makes up roughly one-quarter of the total protein mass [13,14]. Researchers have identified around 20 several types of collagens, with types I, II, III, V, and XI being the most prominent in connective tissues. These five types are classified as fibrillar collagens because they create strand-like structures known as fibrils, which aggregate into large, cable-like bundles. Under light microscopy, these bundles appear as collagen fibres [15,16].

## Types:

The hypermobile form of ED syndrome (hEDS), previously called the hypermobility type or type 3, is believed to be the most prevalent subtype, although its exact incidence remains uncertain. While older studies estimate it affects approximately 1 in 5,000 individuals, this figure is considered outdated, as hEDS and hypermobility spectrum disorders (HSD) frequently go unrecognized or are misdiagnosed as other conditions. Current expert opinion suggests that HSD and possibly hEDS are likely more common than previously thought. It is probable that all EDS subtypes are underdiagnosed to some extent due to a lack of awareness and the complex, overlapping nature of the conditions [17].

There are 13 types of EDS:

- **Arthrochalasia EDS (aEDS):** Arthrochalasia ED syndrome is an exceptionally uncommon type of Ehlers-Danlos syndrome. The condition is characterized by extreme joint hypermobility, stretchable skin, subtle facial abnormalities, and congenital dislocation of both hips. aEDS is triggered by variations in an individual's genetic makeup. Specifically, variations in the COL1A1 or COL1A2 genes are responsible for causing aEDS [18].
- **Brittle cornea syndrome (BCS):** BC Syndrome is an extremely rare form of Ehlers-Danlos syndrome that leads to thin and delicate corneas in affected individuals. This condition arises from genetic variations in specific genes. In particular, alterations in the ZNF469 or PRDM5 genes are linked to BCS. Management of BCS focuses on alleviating the symptoms experienced by the individual [19].
- **Cardiac valvular EDS (cvEDS):** Cardiac-Valvular ED syndrome is a very rare form of Ehlers-Danlos syndrome that results in significant heart valve issues, atrophic scarring, skin hyperextensibility, and joint hypermobility. This condition is linked to genetic variations, specifically in the COL1A2 gene [20].

- **Classical EDS (cEDS):** Classical ED syndrome is an inherited disorder. Genetic testing can now identify the underlying cause in the majority of cEDS patients, with most having variations in the COL5A1 gene. A smaller subset of cEDS individuals carry changes in the COL5A2 gene, while in some cases the genetic Etiology remains unidentified. [21] When a specific gene variation is detected, it allows for targeted genetic testing in other family members. If genetic testing does not provide a clear diagnosis, a skin biopsy may be considered to confirm or exclude cEDS. This procedure involves administering a local anaesthetic to the inner upper arm, followed by removal of a small skin sample. The skin specimen is then examined under an electron microscope for characteristic collagen fibril abnormalities known as "collagen flowers" or "cauliflower fibrils", which are indicative of cEDS [22].
- **Classical-like EDS (clEDS):** Classical-like ED syndrome is an exceptionally rare form of Ehlers-Danlos syndrome that leads to skin hyperextensibility, easy bruising, spontaneous ecchymoses, and generalized joint hypermobility. This condition is attributed to genetic variations, specifically in the TNXB gene [23].
- **Dermatosparaxis (dEDS):** Dermatosparactic ED syndrome is a rare form of Ehlers-Danlos syndrome characterized by extremely loose and fragile skin, significant bruising, and distinctive craniofacial features. This condition results from genetic variations, specifically in the ADAMTS2 gene [24].
- **Hypermobile EDS (hEDS):** Hypermobile ED syndrome, previously referred to as the hypermobility type or type 3, is believed to be the most prevalent genetic connective tissue disorder. Current research does not provide precise information on its prevalence. The condition can be passed down from a parent who carries the same genetic mutation, or it may arise from a new mutation, resulting in the disorder appearing in a family for the first time [25].
- **Kyphoscoliotic EDS (kEDS):** Kyphoscoliotic ED syndrome is an exceptionally rare form of this disease group, which is identified by muscle hypotonia, congenital or early-onset kyphoscoliosis, and generalized joint hypermobility. This condition is related to genetic variations, specifically in the PLOD1 or FKBP14 genes [26].
- **Musculocontractural EDS (mcEDS):** Musculocontractural ED syndrome is an extremely rare type of ED syndrome that presents with congenital multiple contractures, along with distinct cranial and skin characteristics. This condition results from genetic variations, specifically in the CHST14 gene [27].
- **Myopathic EDS (mEDS):** Myopathic ED syndrome is an exceptionally rare form of ED syndrome characterized by muscle atrophy, congenital muscle hypotonia, hypermobility of the hands, and joint contractures. This condition is caused by genetic variations, specifically in the COL12A1 gene [28].
- **Periodontal EDS (pEDS):** Periodontal ED syndrome is an extremely rare type of ED syndrome that leads to early-onset severe periodontitis, characterized by a lack of attached gingiva, first-generation

family members meeting the diagnostic criteria, and the presence of pretibial plaques. This condition arises from genetic variations, specifically in the C1R and C1S genes [29].

- **Spondylodysplastic EDS (spEDS):** Spondylodysplastic ED syndrome is an exceptionally rare form of ED syndrome that results in muscle hypotonia, short stature, and bowed limbs. This condition is linked to genetic variations in the B4GALT7, B3GALT6, and SLC39A13 genes [30].
- **Vascular EDS (vEDS):** Vascular ED syndrome is a serious subtype of a genetic connective tissue disorder. Individuals with this condition have extremely delicate tissues and face a heightened risk of severe bleeding and internal injuries. Although not curable, vEDS can often be managed effectively, with its complications being treatable. In the majority of cases, vEDS is caused by a variation in the COL3A1 gene. In rare instances, it may result from a genetic change in the COL1A1 gene. The inheritance pattern is autosomal dominant [31].

## Etiology

The ED syndromes are a collection of connective tissue disorders stemming from genetic variations (mutations) in different genes. The classical type is typically caused by variants in the COL5A1 or COL5A2 genes, or occasionally in COL1A1. The classical-like type is caused by variants in the TNXB gene, and this gene has also been implicated in a small percentage of hypermobile type cases, although the cause is unknown in most patients with this type. The vascular type is most often caused by COL3A1 variants, with rare cases resulting from certain COL1A1 variants. ADAMTS2 variants cause the dermatosparaxis type, while PLOD1 or FKBP14 variants lead to the kyphoscoliotic type. Other rare forms of ED syndrome are associated with variants in additional genes [32].

## Epidemiology

The precise prevalence of various EDS subtypes remains unclear. A 2019 literature review indicated that most epidemiological data rely on the 1997 classification system, which did not prioritize genetic factors for diagnosis. Hypermobility type EDS is identified as the most prevalent subtype, occurring in approximately 1 in 10,000 to 1 in 15,000 individuals.

The classical type of Ehlers-Danlos syndrome (EDS) is estimated to affect approximately 1 in 10,000 to 1 in 20,000 individuals. In contrast to the more common subtypes, many other variants of EDS are extremely rare. For instance, the kyphoscoliotic type has been documented in around 60 patients, while the dysfibronectinemic type has been reported in only one family. It is essential to recognize that the overall incidence of EDS is likely underestimated. Individuals with milder forms of the condition, characterized by lesser joint or skin involvement, may not face significant clinical symptoms and therefore they might not need medical attention. Even when they do seek help, the subtlety of their symptoms can make diagnosis challenging, and genetic testing may not be considered necessary or pursued [29].

## Signs and symptoms

The clinical presentation of ED syndrome varies significantly depending on the specific subtype involved; nevertheless, there are certain key features that healthcare professionals must recognize and properly evaluate to facilitate diagnosis and guide management. Although the underlying biochemical collagen pathology is present from birth, the clinical manifestations often become evident later in life [32]. Two of the most frequently observed signs of EDS are skin hyperextensibility and joint hypermobility.

Cutaneous manifestations are a hallmark of ED syndrome, with the skin often exhibiting excessive stretchiness, a smooth and velvety texture, fragility, delayed wound healing, and thin, atrophic scarring as common features. Shoulder dislocations can be an early presenting sign of EDS [33]. While the characteristic skin findings provide a key diagnostic criterion, there are no specific laboratory tests to confirm the diagnosis [34].

Patients with ED syndrome frequently exhibits dental issues. The absence of attached gingiva may serve as a distinctive indicator of the condition. Consequently, dentists play a vital role in the early diagnosis and management of these patients [35].

Frequent musculoskeletal manifestations include hypermobility, which can result in recurrent subluxations and dislocations, ultimately leading to early-onset osteoarthritis and chronic pain [36]. Due to the underlying collagen dysfunction, other tissues are prone to fragility, including hollow and solid internal organs [37]. Furthermore, hernias and rectal prolapse are commonly observed in individuals with ED syndrome. The skin typically appears pale and has a soft texture, with underlying blood vessels often becoming visible. It has a doughy consistency and is highly hyperextensible, stretching easily and quickly returning to its original shape once released. Molluscoid pseudotumor, which are small, spongy growths, can develop over scars and pressure points [38]. These are frequently seen in individuals with type I ED syndrome.

## Pathophysiology

ED syndrome is primarily caused by inheritable defects in collagen production or processing, which can be passed down through autosomal dominant or recessive inheritance patterns. Interestingly, spontaneous mutations have also been observed that lead to the same genetic and clinical presentations. The collagens affected by these mutations are essential components of connective tissues throughout the body, from the skin to the blood vessels. As a result, EDS can manifest with diverse symptoms depending on which tissues are impacted by the specific collagen defect [39].

Mutations in collagen genes and related enzymes underlie the pathogenesis of various Ehlers-Danlos syndrome (EDS) subtypes. The vascular type (IV) is characterized by reduced type III collagen due to mutations in the *COL3A1* gene, leading to weakened connective tissues and life-threatening complications like arterial, uterine, and intestinal ruptures. Types V and VI are caused by deficiencies in enzymes crucial for collagen post-translational modifications, such as hydroxylase and lysyl oxidase. Type VII is defined by a deficiency in the

amino-terminal procollagen peptidase. Abnormal copper metabolism and nonfunctional plasma fibronectin underlie types IX and X, respectively. In the classical types I and II EDS, causative mutations may involve the *COL5A1*, *COL5A2*, and *tenascin-X* genes, with a suggested role for *COL1A2*. However, in most autosomal dominant EDS cases, the disease is linked to loci containing the *COL5A1* or *COL5A2* genes [40].

## Diagnosis

The diagnosis of ED syndrome primarily relies on recognizing a constellation of characteristic symptoms. Once EDS is suspected, the initial evaluation should focus on the specific systems affected to determine if the presentation is consistent with the disorder. After an EDS diagnosis is made, the subsequent workup aims to assess the extent of systemic involvement. For classic-type EDS, Malfait et al. recommend a thorough skin examination followed by applying the Beighton criteria to assess joint hypermobility. In young patients, an assessment of motor development is important. Additionally, a baseline echocardiogram is advised for children under 10 years old. If easy bruising is a prominent feature, evaluating coagulation factors may be warranted to rule out a concomitant bleeding disorder [41].

Skin hyperextensibility is assessed and distinguished from conditions like cutis laxa by confirming that the skin, when stretched, quickly returns to its original shape after being released. When Ehlers-Danlos syndrome (EDS) is suspected, imaging techniques such as CT scans, MRIs, and echocardiograms can be employed to investigate common cardiovascular issues, including mitral valve prolapse and aortic dilation [42].

## Management

ED syndrome currently has no known cure, and treatment primarily focuses on supportive care. Managing the condition involves close monitoring of cardiovascular health, as well as physiotherapy and occupational therapy. These interventions can enhance joint stability and help prevent injuries. To mitigate the risk of joint damage, individuals with EDS are advised to avoid activities that may lead to joint locking or overextension. In some cases, a physician might recommend casting to stabilize affected joints. Referrals to orthotists for bracing and to physical or occupational therapists for muscle strengthening and joint preservation techniques are also common. These strategies aim to improve quality of life and reduce the likelihood of further complications associated with the syndrome [43].

Medical treatment for Ehlers-Danlos syndrome (EDS) is primarily focused on alleviating symptoms. Prior to pregnancy, individuals with EDS are often advised to seek genetic counseling to understand the potential risks associated with pregnancy. It is essential for children diagnosed with EDS to receive education about their condition, enabling them to comprehend the importance of avoiding contact sports and other physically demanding activities. They should also be cautioned against demonstrating their ability to hold unusual joint positions, as this can lead to premature joint degeneration [44]. In addition to physical support, emotional and psychological assistance can be beneficial. Support groups are valuable resources for individuals facing significant lifestyle adjustments and health challenges [45].

**Pain management**

Effective management of chronic pain in individuals with ED syndrome necessitates a multidisciplinary approach. Pain management strategies may need to be adapted from those typically used for the general population. Pain can be categorized into different types, including nociceptive pain, which arises from tissue injuries, and neuropathic pain, which results from abnormal nerve signals [45]. Often, individuals experience a combination of both types of pain. Physiotherapy, particularly exercise rehabilitation, plays a crucial role in managing pain by focusing on core and joint stabilization. Stretching exercises should be approached with caution, emphasizing polite and easy movements to minimize the risk of dislocations or subluxations [46].

**Medication**

Chronic pain associated with Ehlers-Danlos syndrome (EDS) requires a comprehensive treatment approach involving various healthcare professionals. Pain management strategies may need to be tailored to the specific needs and symptoms of individuals with EDS. Pain can be categorized based on its underlying cause, such as nociceptive pain resulting from tissue damage or neuropathic pain arising from abnormal nerve signals. In many cases, individuals with EDS experience a combination of these pain types. Physiotherapy, particularly exercise rehabilitation, is a crucial component of pain management in EDS. Physiotherapists focus on stabilizing the core and joints through targeted exercises. However, it is essential to approach stretching exercises cautiously, emphasizing casual movements to minimize the risk of joint dislocations or subluxations [47].

**Surgery**

Common surgical interventions for Ehlers-Danlos syndrome (EDS) include joint debridement, tendon replacements, capsulorrhaphy, and arthroplasty. While these procedures may enhance stabilization, reduce pain, and improve patient satisfaction, they do not always yield optimal results, and both patients and surgeons have reported dissatisfaction with outcomes. Generally, conservative treatments are considered more effective than surgical options, particularly because individuals with EDS face heightened risks of surgical complications due to the nature of the condition [48]. Three primary surgical challenges associated with EDS include: the weakened state of connective tissues, which makes them less amenable to surgical procedures; the weakness of blood vessels, which can lead to complications during surgery; and delayed or incomplete wound healing. Therefore, if surgical intervention is contemplated, it is advisable to consult a surgeon who has significant experience and knowledge to treat patients with EDS and related joint hypermobility problems [49].

## Patient's unmet needs

In 2017, the classification of Ehlers-Danlos syndrome (EDS) was revised to include 13 distinct and rare hereditary connective tissue diseases, with prevalence rates ranging from approximately 1 in 5,000 to extremely rare types affecting only a handful of individuals or families worldwide. An additional type was introduced in 2018. Despite this updated classification raising awareness about EDS, many patients still face difficulties in obtaining timely and accurate diagnoses and treatments. A significant number of healthcare providers lack

training in recognizing EDS or understanding how to manage it effectively. In numerous European countries and beyond, there is a scarcity of diagnostic centers and specialists available to assist patients [50]. The lack of educational resources for both healthcare professionals and patients contributes to numerous unmet needs in this area. Patients with EDS frequently experience generalized joint hypermobility, chronic pain, and weakness. Managing pain can be difficult and typically needs the support of specialized pain clinics and integrated rehabilitation programs [51]. Clinical observations suggest that medical marijuana might serve as a viable alternative to opioids for pain relief; however, access to this treatment is limited in many EU countries.

## Conclusion

This review highlights the significant absence of high-quality clinical practice guidelines (CPGs) for ED syndrome (EDS) and identifies numerous unmet needs for both healthcare providers and patients. The lack of definitive diagnostic tests for certain subtypes like hypermobile EDS (hEDS), coupled with the involvement of multiple body systems and chronic pain, underscores the need for a multidisciplinary approach to patient care. Ongoing research is crucial to elucidate the underlying genetic and molecular mechanisms, develop targeted therapies, and improve the quality of life for individuals living with EDS. As our understanding of this syndrome evolves, it is essential to foster collaboration among healthcare professionals, including geneticists, rheumatologists, pain specialists, and mental health providers, to deliver comprehensive care that addresses the diverse necessities of EDS patients.

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