https://repository.uaeh.edu.mx/revistas/index.php./MJMR/issue/archive

Mexican Journal of Medical Research ICSa

Biannual Publication, Vol. 14, No.28 (2026) 1-8

ISSN: 2007-5235

A Narrative Review of Hypermobile Ehlers-Danlos Syndrome: Diagnostic Challenges and Opportunities in Primary Care

Revisión narrativa sobre el síndrome de Ehlers-Danlos hipermóvil: desafíos y oportunidades diagnósticas en atención primaria

Doris del Carmen Pinto-Escalante[a], Martín Rodríguez-Alvarado[b], Silvina Contreras-Capetillo[c], Lizbeth González-Herrera[d], Rodrigo Rubi-Castellanos[e]

Abstract:

Hypermobile Ehlers-Danlos syndrome (hEDS), an autosomal dominant condition, is the most common subtype of hereditary connective tissue disorders. It represents a diagnostic challenge in primary care due to its variable phenotype, multisystemic involvement, and the absence of an associated gene. This narrative review aims to show the existing evidence for its clinical recognition, promote a multidisciplinary approach, and highlight its relevance in primary care to improve comprehensive management. Based on the diagnostic criteria established by an international consortium in 2017 and considering the lack of a specific management guideline, a review of the updated information on the clinical manifestations of hEDS was carried out. This analysis focused on identifying aspects that could facilitate early detection at the primary care level, including differential diagnoses and the diverse multisystemic presentations of of hEDS across the lifespan. The role of primary care physician in identifying these cases, as well as their multidisciplinary management and referral according to clinical manifestations, is emphasized. Early recognition of hEDS can reduce years of medical referrals and significantly improve patients' quality of life.

Keywords:

Hypermobile Ehlers-Danlos syndrome, joint hypermobility, clinical diagnosis, autosomal dominant, primary care, connective tissue disorders, rare diseases, family medicine.

Resumen:

El síndrome de Ehlers-Danlos hipermóvil (hEDS), una condición autosómica dominante, es el subtipo más frecuente de los trastornos hereditarios del tejido conectivo. Representa un desafío diagnóstico en el primer nivel de atención por su fenotipo variable, afectaciones multisistémicas y por carecer de un gen asociado. Esta revisión narrativa tiene como objetivo mostrar la evidencia existente para su reconocimiento clínico, promover un enfoque multidisciplinario y destacar su relevancia en el primer nivel de atención médica para mejorar su manejo integral. Con base en los criterios diagnósticos establecidos por un consorcio internacional en 2017, y considerando la ausencia de una guía de manejo específica, se llevó a cabo una revisión de la información actualizada sobre las manifestaciones clínicas del hEDS. Este análisis se centró en identificar los aspectos que podrían facilitar la detección precoz en el primer nivel de atención, incluyendo los diagnósticos diferenciales y las diversas expresiones multisistémicas del hEDS a lo largo de la vida. Se enfatiza el papel del médico de primer nivel en la identificación de estos casos, así como su manejo multidisciplinario y derivación acorde con las manifestaciones clínicas. El reconocimiento temprano del hEDS puede reducir años de interconsultas médicas y mejorar significativamente la calidad de vida de los pacientes.

***Palabras Clave**:*

Síndrome de Ehlers-Danlos hipermóvil, hipermovilidad articular, diagnóstico clínico, autosómica dominante, atención primaria, enfermedades del tejido conectivo, enfermedades raras, medicina familiar

[a] Centro de Investigaciones Regionales Dr Hideyo Noguchi, Universidad Autónoma de Yucatán, Mérida, Yucatán, México, https://orcid.org/0000-0002-5220-4246, Email: pescalan@correo.uady.mx

[b] Licenciatura en Médico Cirujano y Partero, Instituto Politécnico Nacional, Ciudad de México, México, https://orcid.org/0009-0008-9307-4223, Email: martinrodriguezalvarado61@gmail.com

[c] Centro de Investigaciones Regionales Dr Hideyo Noguchi, Universidad Autónoma de Yucatán, Mérida, Yucatán, México, https://orcid.org/0000-0003-3338-3813, Email: silvina.contreras@correo.uady.mx

[d] Centro de Investigaciones Regionales Dr Hideyo Noguchi, Universidad Autónoma de Yucatán, Mérida, Yucatán, México, https://orcid.org/0000-0002-8620-3954, Email: lizbeth@correo.uady.mx

[e] Corresponding author, Centro de Investigaciones Regionales Dr Hideyo Noguchi, Universidad Autónoma de Yucatán, Mérida, Yucatán, México, https://orcid.org/0000-0002-5990-8326, Email: rodrigo.rubi@correo.uady.mx

Received: 08/11/2025, Accepted: 21/01/2026, Postprint: 30/01/2026, Published: 05/07/2026

DOI: https://doi.org/10.29057/mjmr.v14i28.16512

INTRODUCTION

Ehlers-Danlos syndromes (EDS) comprise a clinically and genetically heterogeneous group of hereditary connective tissue disorders, characterized by generalized joint hypermobility, skin hyperextensibility, tissue fragility, and a broad spectrum of systemic manifestations.[1] In 2017, the International Consortium on Ehlers-Danlos Syndromes established a new classification defining 13 EDS subtypes, based on clinical, molecular, and genetic criteria.[1,2] Among these, the hypermobile subtype (hEDS)—listed in the Online Mendelian Inheritance in Man database (OMIM 130020) and in the international reference portal for rare diseases and orphan drugs (Orphanet; ORPHA code 285)—is the most common. Nevertheless, its diagnosis remains a clinical challenge, particularly in primary care settings, as its clinical features may be mistaken for more common musculoskeletal conditions or functional disorders. This is compounded by the absence of a confirmatory genetic test[2,3], making its identification reliant solely on clinical criteria. In this context, the primary care physician plays a crucial role as a facilitator of timely diagnosis and coordinator of multidisciplinary management. The absence of a confirmatory genetic test and the widespread lack of awareness among healthcare professionals regarding the clinical variability of the syndrome further reinforce diagnostic delays.[4,5] As a result, patients often spend years navigating multiple medical specialties, receiving incorrect diagnoses and symptomatic treatments that fail to address the underlying condition.[5,6]

This narrative review contextualizes the current evidence for hEDS with the aims of providing first-contact physicians a practical clinical tool and a comprehensive perspective of the disease. It addresses its clinical manifestations, current diagnostic criteria, relevant differential diagnoses, and a system-based description grounded in the latest scientific evidence. Furthermore, it seeks to raise awareness among healthcare professionals about the importance of recognizing this multisystemic and frequently underdiagnosed condition, promoting person-centered, empathetic, coordinated, and evidence-based care that meets the real needs of patients from the first point of contact.

PREVALENCE

The prevalence of hEDS remains uncertain. Population-based studies applying the diagnostic criteria established in 2017 are scarce, making it difficult to accurately estimate its frequency. According to ORPHANET (ORPHA:285), prevalence is estimated to range between 1:5,000 and 1:20,000, with a predominance in women. To date, there are no population-based studies in Mexico reporting the prevalence of hEDS. However, recent research in the United Kingdom has reported higher figures, such as 1:3,100[7], suggesting that hEDS may be significantly underdiagnosed. This underestimation is related to the wide phenotypic variability of the syndrome and the nonspecific nature of its clinical manifestations, which may be attributed to various etiologies. In non-specialized settings, this complicates recognition and favors more common alternative diagnoses. Additionally, the presence of chronic musculoskeletal pain and psychiatric symptoms such as anxiety or somatization may divert clinical attention toward more frequent disorders, contributing to the invisibility of hEDS in general medical practice.

PHENOTYPE

Clinically, hEDS is characterized by generalized joint hypermobility, chronic musculoskeletal pain, joint instability, and persistent fatigue.[2,4,8] Additionally, autonomic symptoms such as syncope, orthostatic intolerance, and postural orthostatic tachycardia syndrome (POTS) are commonly observed.[9] Functional gastrointestinal disorders have also been described, including dyspepsia, constipation, and early satiety.[10] In the neuropsychiatric domain, associations with generalized anxiety, depression, and sleep disturbances have been documented, reflecting the systemic and psychosocial impact of the syndrome.[11] This multisystemic clinical expression contributes to diagnostic fragmentation and underscores the need for a comprehensive evaluation, particularly at the primary care level, where healthcare professionals can integrate these findings and appropriately guide the diagnostic and therapeutic approach.[2,12]

INITIAL EVALUATION AND DIAGNOSIS

Given the clinical complexity of hEDS, the role of primary care physician is fundamental. Applying the clinical diagnostic criteria established in 2017[1], along with the systematic use of the Beighton score to assess joint hypermobility[3,13,14], enables the primary care provider to suspect this condition. A system-oriented clinical examination that considers the variability of multisystemic manifestations facilitates the identification of patterns consistent with hEDS. Diagnostic suspicion, the exclusion of common pathologies, and timely referral to medical specialties such as clinical genetics and rheumatology are key steps toward achieving a definitive diagnosis. Furthermore, coordination with other specialties—dermatology, psychiatry, nutrition, physical medicine and rehabilitation, cardiology, neurology, among others—based on each patient's specific needs, promotes a comprehensive and person-centered approach.

DIAGNOSTIC CRITERIA FOR hEDS

The 2017 international consensus updated the classification of Ehlers-Danlos syndrome subtypes, establishing that the hypermobile type (hEDS) is diagnosed exclusively through clinical evaluation and by ruling out other conditions, unlike other subtypes that rely on genetic confirmation.[1] According to an

update from The Ehlers-Danlos Society, over 99 % of their study participants fulfilled the current clinical criteria for hEDS. Fewer than 1% showed genetic variants suggestive of other connective tissue disorders, underscoring the validity and importance of these guidelines.[15]

Table 1. *Diagnostic criteria for hEDS.*[1,16]

Criterion	Description	Condition to Fulfill
1. Generalized Joint Hypermobility (GJH)	Assessed using the Beighton score, adjusted for age and sex.	Score ≥5 in adults <50 years; ≥4 in adults ≥50 years. If not met, historical evidence may be considered.
2. Clinical manifestations consistent with hEDS	At least 2 of the following 3 features must be met:	
A. Systemic signs of a connective tissue disorder	Soft skin, atrophic stretch marks, flat feet, hernias, dysautonomia, fatigue, gastrointestinal disorders, slow wound healing, proprioceptive alterations.	At least 5 positive signs required.
B. Recurrent musculoskeletal manifestations	Chronic pain, frequent dislocations or subluxations.	At least one must be present.
C. Family history of hEDS	Confirmed diagnosis in a first-degree relative.	Documented clinical evidence.
3. Exclusion of other conditions	Other EDS subtypes, hereditary connective tissue disorders, and syndromes with secondary hypermobility must be ruled out.	Clinical and genetic evaluation as available.

* Clinical evaluation should consider the patient's age, sex, and individual context.

To confirm the diagnosis, three criteria must be met:

1. Generalized Joint Hypermobility (GJH).
2. Clinical manifestations consistent with hEDS (at least two of the A, B, and C features).
3. Exclusion of other connective tissue disorders.

Within the feature B, at least five systemic signs are expected for the component to be considered positive (see Table 1).[1,16] This diagnostic structure highlights the need for a comprehensive clinical evaluation from the first medical contact.

DIFFERENTIAL DIAGNOSES

In the absence of a confirmatory genetic test, the diagnosis of hEDS requires the exclusion of other conditions with similar phenotypes.[1] The most relevant differential diagnoses in clinical practice are presented in Table 2.[12,16–18]

Table 2*. Descriptive elements to perform differential diagnoses with hEDS.*[12,16-18]

Condition	OMIM ORPHA	Gene(s) Involved	Key Clinical Features	Main Clinical Risks
cEDS	130000 287	*COL5A1*, *COL5A2*	Skin hyperextensibility, atrophic scars, frequent bruising	Skin fragility, surgical complications
vEDS	130050 286	*COL3A1*	Characteristic facial features, translucent skin, spontaneous rupture of vessels, uterus, and intestines	Spontaneous arterial, visceral, and uterine rupture
kEDS	225400 1900	*PLOD1*, *FKBP14*	Congenital hypotonia, early-onset scoliosis, severe myopia	Progressive scoliosis, motor disability
Marfan Syndrome	154700 558	*FBN1*	Tall stature, marfanoid habitus, ectopia lentis, aortic dilation	Aortic aneurysm, aortic dissection
Loeys-Dietz Syndrome	609192 60030	*TGFBR1*, *TGFBR2*	Hypertelorism, bifid uvula, early aneurysms, fragile skin	Cerebral, aortic, and visceral aneurysms
Osteogenesis Imperfecta	166200 216796	*COL1A1*, *COL1A2*	Multiple fractures, blue sclerae, dentinogenesis imperfecta	Recurrent fractures, bone deformities
hEDS	130020 285	Not identified	Joint hypermobility, chronic pain, dysautonomia, gastrointestinal and psychiatric symptom	Functional disability, chronic pain, psychosocial impact

* EDS: Ehlers-Danlos Syndrome. cEDS: Classical EDS. vEDS: Vascular EDS. kEDS: Kyphoscoliotic EDS. hEDS: Hypermobile EDS. Differential diagnosis of hEDS with other hereditary connective tissue disorders. OMIM (https://www.omim.org/) and ORPHANET (https://www.orpha.net/es/disease) identifiers are included to facilitate consultation in specialized databases, along with implicated genes, key clinical manifestations, and main clinical risks. This comparison helps guide diagnostic suspicion and supports timely referral to clinical genetics in cases with overlapping phenotypes.

hEDS overlaps clinically with other hereditary connective tissue disorders, such as Marfan syndrome, Loeys-Dietz syndrome, and other EDS subtypes, including classical (cEDS) and vascular (vEDS) forms.[16–18] These conditions may share features such as joint hypermobility, valvular prolapse, dysautonomia, skeletal abnormalities, and tissue fragility; however, they differ

significantly in prognosis and the risk of serious complications, such as aortic aneurysms or spontaneous visceral ruptures.[16,18] Clinical differentiation requires a systematic evaluation of multisystemic findings, family history, and the application of specific criteria, such as those established in the 2017 international classification. In this context, tools such as the Beighton score, the five-item questionnaire, and targeted examination of cutaneous, cardiovascular, and skeletal signs are essential for guiding the differential diagnosis.[19,20]

The Beighton score is a standardized tool for assessing joint hypermobility. It consists of nine points distributed across five specific maneuvers. Its interpretation must be adjusted for age and sex, as hypermobility tends to decrease with age. In adults under 50 years, a score ≥5 is considered indicative of generalized joint hypermobility; in adults aged 50 and older, the threshold is reduced to ≥4. In cases where the required score is not met, historical evidence of hypermobility may be considered, such as a history of physical activities involving extreme flexibility (e.g., dance, gymnastics, yoga).[13,20,21]

The five-item questionnaire is a useful screening tool for identifying joint hypermobility in adults, especially when the Beighton score cannot be directly applied. It includes questions about personal history of extreme flexibility, dislocations, ease in performing highly mobile postures, and family history. A positive result (≥2 affirmative answers) suggests generalized joint hypermobility and may support the diagnostic suspicion of hEDS.[19]

These tools help distinguish hEDS from other hereditary connective tissue disorders that share manifestations such as joint hypermobility, chronic musculoskeletal pain, or cardiovascular abnormalities.

CLINICAL PHENOTYPE BY SYSTEMS

hEDS exhibits a highly heterogeneous clinical phenotype, with manifestations that evolve with age and affect multiple systems, making its recognition challenging. The following section provides an overview of the main clinical features organized by system (Table 3).

Musculoskeletal System

Musculoskeletal manifestations are the clinical core of hEDS and represent one of the main reasons for medical consultation. Chronic pain, typically nociplastic in nature, is often diffuse, migratory, and persistent, with exacerbations related to physical exertion or joint instability. The latter, a product of ligamentous laxity, predisposes to recurrent dislocations and subluxations, especially in joints of the shoulders, knees, and ankles.

Table 3. *Clinical Manifestations of hEDS by System.*[4,5,9-11,21-29]

System	Clinical Manifestations	Supporting Specialties
Musculo-skeletal	- Chronic musculoskeletal pain (nociplastic, diffuse, migratory) - Frequent dislocations and subluxations (shoulders, jaw, fingers) - Flat feet, hyperlordosis, mild scoliosis - Joint hyperlaxity - Muscle fatigue - Fine motor delay - Proprioceptive alterations - Muscle weakness	Physical medicine and rehabilitation, rheumatology, psychology/psychiatry
Skin and Connective Tissue	- Soft, silky, velvety skin - Moderate skin hyperextensibility - Thin, translucent skin (visible venous network) - Atrophic stretch marks without weight changes - Skin fragility with spontaneous bruising - Abnormal scarring - Raynaud's phenomenon and chilblains	Dermatology
Cardio-vascular	- Palpitations - Orthostatic intolerance - Vasovagal syncope - Dyspnea - Mitral valve prolapse - Mild aortic dilation	Cardiology
Autonomic (Dysautonomia)	- Postural orthostatic tachycardia syndrome (POTS) - Neurocardiogenic syncope - Orthostatic hypotension - Heat and exercise intolerance - Excessive sweating - Chronic fatigue	Neurology
Gastro-intestinal	- Gastroesophageal reflux - Chronic constipation - Dyspepsia - Early satiety - Food intolerance - Possible gastroparesis and intestinal dysmotility	Gastro-enterology
Psychiatric and Neuro cognitive	- Generalized anxiety - Depression secondary to chronic pain - Sleep disorders - Somatization - Heightened bodily awareness - Medical frustration due to diagnostic delay	Psychiatry

*Clinical manifestations of hEDS organized by systems. The main musculoskeletal, cutaneous, cardiovascular, autonomic, gastrointestinal, and neuropsychiatric findings are summarized, highlighting their diagnostic relevance and functional impact on the patient's life.

Additionally, a high prevalence of proprioceptive alterations, muscle weakness, and fatigue has been documented, contributing to progressive functional deterioration.[4,6,21,22] In this context, the physician plays a key role in the early recognition of chronic pain as a cardinal manifestation of hEDS. A biopsychosocial approach allows addressing not only the physical component of pain but also its emotional and social impact. Through longitudinal follow-up, the physician can coordinate non-pharmacological interventions such as individualized physical therapy, self-care education, and psychological support, avoiding excessive medicalization and promoting person-centered strategies.

Skin and Connective Tissue

Cutaneous manifestations for hEDS reflect collagen dysfunction in the extracellular matrix. Although they are less severe than other EDS subtypes of hEDS, their presence can guide the clinician when accompanied by musculoskeletal and systemic findings. Notable features include soft or velvety skin, skin fragility, and abnormal scarring.[23]

Dermatologic management should consider susceptibility to injury, avoiding unnecessary invasive procedures, minimizing the use of topical steroids, and promoting preventive skin care. These alterations may be related to extracellular matrix dysfunction and mast cell-mediated inflammatory processes, which could explain symptoms such as urticaria, pruritus, and recurrent facial flushing.[24]

Cardiovascular System

Cardiovascular manifestations, although generally not life-threatening, can cause significant symptomatic burden. Common findings include orthostatic hypotension, palpitations, vasovagal syncope, and dyspnea, often in the context of dysautonomia. A survey-based study of patients with hEDS and hypermobility spectrum disorders found that over 80% presented symptoms compatible with orthostatic intolerance, highlighting the importance of their systematic evaluation in general medical practice. While mild aortic dilation and mitral valve prolapse may be observed, their frequency is lower than in other EDS subtypes and their course is usually benign.[23]

Autonomic System (Dysautonomia)

Autonomic dysfunction is a frequent and debilitating manifestation in hEDS, with significant impact on quality of life. Common syndromes include postural orthostatic tachycardia syndrome (POTS), neurocardiogenic syncope, and orthostatic hypotension, accompanied by symptoms such as palpitations, heat and exercise intolerance, excessive sweating, and chronic fatigue. A clinical triad composed of dysautonomia, hypermobility spectrum disorders, and mast cell activation syndrome (MCAS) suggests a pathophysiological interaction between autonomic regulation, extracellular matrix, and neurogenic inflammation.[9,24,25] These symptoms are often misattributed to functional or psychogenic causes.

Gastrointestinal System

Gastrointestinal manifestations in hEDS are frequent and multifactorial. Functional symptoms predominate, such as dyspepsia, early satiety, chronic constipation, and gastroesophageal reflux, related to intestinal motility disorders, visceral hypotonia, and dysautonomia. These patients are often diagnosed with irritable bowel syndrome. One study reports that gastrointestinal dysfunction, including gastroparesis and poor tolerance to enteral feeding, may reflect systemic involvement of the gut-brain axis, especially in chronic or critical illness contexts. Although the study focuses on hospitalized patients, its findings on the relationship between dysmotility, inflammation, and feeding tolerance are applicable to hEDS patients.[10,25,26] This reinforces the need for functional assessment and individualized nutritional support.

Psychiatric and Neurocognitive Manifestations

Neuropsychiatric alterations in hEDS include generalized anxiety, depression, sleep disorders, and heightened bodily awareness. These manifestations are associated with chronic pain, dysautonomia, and diagnostic delay, and can significantly affect quality of life. Increased perception of physical discomfort and medical frustration contribute to the emotional burden of the patient. Individuals with multisystemic conditions such as hEDS are more vulnerable to mood disorders, reinforcing the need for comprehensive evaluation.[5,11,27–29]

Natural History

hEDS presents a multisystemic clinical progression that varies throughout the life cycle. Although the course is not uniform across patients, a general chronology has been described that helps visualize the clinical trajectory of the syndrome and plan preventive, diagnostic, and therapeutic interventions from the primary care level (Table 4).

During childhood and adolescence, motor and musculoskeletal signs predominate, such as joint hypermobility, frequent falls, fatigue, and nonspecific pain. These symptoms often go unnoticed or are attributed to developmental variants, leading to fragmented approaches that fail to integrate a syndromic view.[8,30,32]

In youth and early adulthood, the cardinal manifestations of hEDS become more consolidated, including chronic pain, dysautonomia, functional gastrointestinal symptoms, and neuropsychiatric alterations. This stage often coincides with an increase in functional and emotional burden, requiring a biopsychosocial approach that includes longitudinal support and interdisciplinary coordination.[31]

Table 4: *Natural evolution of hEDS by life stages.*[8,30-32]

Life Stage	Predominant Clinical Manifestations	Biopsychosocial Effects
Childhood and Adolescence **0-20 years**	- Mild psychomotor delay - Hypotonia, motor clumsiness - Joint pain ("growing pains") - Dislocations/subluxations - Early stretch marks - Headaches - Functional constipation - Easy fatigue	School, sports, and social difficulties.
Youth and Early Adulthood **20-40 years**	- Chronic musculoskeletal pain - Persistent fatigue - Dysautonomia (POTS, syncope) - Functional gastrointestinal disorders - Anxiety, depression - Joint instability - Pelvic/bladder dysfunction	Medical frustration and somatization Anxiety and depression. Impact on education and employment.
Middle and Late Adulthood **40 years and older**	- Progressive joint stiffness - Generalized pain - Increased risk of falls - Mitral valve prolapse, mild aortic dilation - Accumulated emotional impact - Progressive functional disability	Decreased quality of life Psychiatric comorbidities.

* Clinical Evolution of hEDS Across Life Stages. This section describes the predominant manifestations at each stage, from childhood to late adulthood, highlighting their progression and functional impact.

In middle and late adulthood, some patients experience a transition toward joint stiffness, reduced hypermobility, and progressive functional decline. This phase demands an approach focused on functionality, self-care, and comorbidity prevention, with emphasis on rehabilitation, pain management, and psychosocial support.[31]

Understanding this clinical evolution is essential, as it allows for anticipating needs and promoting person-centered management strategies tailored to each stage of life.

IMPORTANCE FOR PRIMARY AND SECONDARY HEALTH CARE LEVELS

The primary care physician plays a fundamental role in the early identification and initial management of hEDS. When faced with a young patient presenting with chronic pain, fatigue, joint hypermobility, and multisystem functional symptoms, they should be able to suspect the diagnosis and systematically apply current clinical criteria. This is particularly relevant given the heterogeneous presentation of hEDS, the absence of genetic markers that confirm the diagnosis, and the limited awareness of low-prevalence genetic diseases, which often results in underdiagnosis and delayed care.[18,32,33]

The use of the Beighton score, combined with a comprehensive clinical evaluation, helps reduce underdiagnosis and coordinate ongoing patient management.[1,13] Additionally, the physician should facilitate timely referrals to specialties such as clinical genetics, rheumatology, physical therapy, nutrition, cardiology, neurology, psychiatry, gastroenterology, and dermatology, depending on the predominant manifestations.[32-34] Coordinating multiple specialties allows for a comprehensive approach that addresses both physical symptoms and the psychosocial impact of hEDS, ensuring continuous and effective care.

In primary care, regular monitoring of pain, safe analgesic use, physical therapy, and relaxation techniques contribute to patient well-being. Mobility control and injury prevention through adapted physical activity, along with education on joint protection strategies, are essential to improve quality of life. Primary care providers also play a key role in patient education and emotional support, mitigating the impact of diagnostic delays. Empathetic, validating, and person-centered care is essential to reduce the clinical, emotional, and social consequences of the diagnostic odyssey often experienced by these patients.

In secondary care, specialists play a critical role in confirming the diagnosis, managing complications, and implementing individualized treatment plans. Effective collaboration among genetics, cardiology, orthopedics, neurology, and rehabilitation services is essential to address multisystem involvement and prevent severe complications such as aortic aneurysms or spontaneous visceral ruptures. This multidisciplinary model, supported by continuous communication between primary and secondary care, is key to providing comprehensive, patients-centered care across all age groups.

The prognosis of hEDS is highly variable and primarily affects quality of life rather than life expectancy. Unlike vascular EDS, which carries a significant risk of arterial rupture and reduced survival, hEDS rarely compromises longevity.[1,18] However, its heterogeneous presentation, chronic pain, fatigue, and multisystem involvement often lead to functional limitations and psychosocial consequences.[4,5,11] Early recognition and multidisciplinary management—including pain monitoring, adapted physical activity, and psychosocial support—can significantly improve patient outcomes.[4,29-31] Although no curative treatment exists, interventions such as physical therapy, safe analgesics, and lifestyle modifications help maintain functionality and reduce symptom burden. In this context, primary care plays a pivotal role in longitudinal follow-up and coordination of specialized care to mitigate disability and enhance quality of life.

CONTINUING MEDICAL EDUCATION

Continuing medical education is essential to improve the recognition, management, and follow-up of rare conditions such as hEDS. Given its clinical complexity and phenotypic variability, healthcare professionals require ongoing updates on diagnostic criteria, assessment tools, and interdisciplinary approaches.[35] Incorporating content on rare diseases into continuing medical education programs helps reduce diagnostic delays, prevent fragmented care, and strengthen problem-solving capacity. It also fosters a culture of informed clinical suspicion, promotes timely referrals to clinical genetics and other specialties, and contributes to more equitable and efficient care for patients with underrecognized diseases. Raising awareness about hEDS and other rare diseases should be part of health education strategies, especially in primary care. This not only improves detection and clinical management but also strengthens the physician-patient relationship and promotes care centered on dignity, respect, and understanding of human suffering.[35]

CONCLUSIONS

Hypermobile Ehlers-Danlos syndrome (hEDS) is a relevant clinical challenge due to its multisystemic nature, the absence of confirmatory genetic markers, and its high rate of underdiagnosis. However, it can be identified through careful clinical evaluation based on updated diagnostic criteria and a comprehensive view of the patient.

Timely diagnosis can reduce years of physical and emotional suffering, avoiding prolonged journeys through multiple specialties and inadequate symptomatic treatments. In this context, the primary care physician plays a key role in early recognition, longitudinal accompaniment, and coordination of a multidisciplinary, person-centered approach.

The quality of life of patients with hEDS can significantly improve when management strategies integrate physical, emotional, and psychosocial treatment. To achieve this, it is essential to strengthen medical education in clinical genetics and connective tissue disorders, especially within family medicine.

It is recommended to promote educational programs, clinical guidelines, and support tools that enhance knowledge of hEDS from the primary care level. Likewise, it is necessary to encourage clinical, epidemiological, and psychosocial research on this condition, with the aim of reducing diagnostic delays and improving comprehensive care for affected individuals.

REFERENCES

[1] Malfait F, Francomano CA, Byers PH, Belmont J, Berglund B, Blackstone C, et al. The 2017 international classification of the Ehlers-Danlos syndromes. Am. J. Med. Genet. C. Semin. Med. Genet. 2017; 175(1): 8–26.

[2] Tinkle B, Castori M, Berglund B, Cohen H, Grahame R, Kazkaz H, et al. Hypermobile Ehlers-Danlos syndrome (hEDS): the need for recognition. Am. J. Med. Genet. C. 2017; 175(1): 48–69.

[3] Castori M, Tinkle B, Levy H, Grahame R, Malfait F, Hakim A. A framework for the classification of joint hypermobility and related conditions. Am. J. Med. Genet. C. 2017; 175(1): 148–57.

[4] Chopra P, Tinkle B, Hamonet C, Brock I, Gompel A, Bulbena A, et al. Pain management in the Ehlers–Danlos syndromes. Am. J. Med. Genet. C. 2017; 175(1): 212–9.

[5] Bulbena A, Baeza-Velasco C, Bulbena-Cabré A, Pailhez G, Critchley H, Chopra P, et al. Psychiatric and psychological aspects in the Ehlers–Danlos syndromes. Am. J. Med. Genet. C. 2017; 175(1): 237–45.

[6] Garreth Brittain M, Flanagan S, Foreman L, Teran-Wodzinski P. Physical therapy interventions in generalized hypermobility spectrum disorder and hypermobile Ehlers-Danlos syndrome: a scoping review. Disabil. Rehabil. 2024; 46(10): 1936-53.

[7] Demmler JC, Atkinson MD, Reinhold EJ, Choy E, Lyons RA, Brophy ST, et al. Diagnosed prevalence of Ehlers–Danlos syndrome and hypermobility spectrum disorder in Wales, UK: a population-based study and case–control comparison. BMJ. Open. 2019; 9(11): e031365.

[8] Tofts LJ, Simmonds J, Schwartz SB, Grahame R, Malfait F, Hakim A, et al. Pediatric joint hypermobility: a diagnostic framework and narrative review. Orphanet J. Rare Dis. 2023; 18(1): 104.

[9] Celletti C, Camerota F, Castori M, Censi F, Gioffrè L, Calcagnini G, et al. Orthostatic Intolerance and Postural Orthostatic Tachycardia Syndrome in Joint Hypermobility Syndrome/Ehlers-Danlos Syndrome, Hypermobility Type: Neurovegetative Dysregulation or Autonomic Failure? Biomed. Res. Int. 2017; 2017: 9161865.

[10] Lam C, Amarasinghe G, Zarate-Lopez N, Fikree A, Byrne P, Kiani-Alikhan S, et al. Gastrointestinal symptoms and nutritional issues in patients with hypermobility disorders: assessment, diagnosis and management. Frontline Gastroenterol. 2022; 14(1): 68-77.

[11] Bulbena-Cabré A, Baeza-Velasco C, Rosado-Figuerola S, Bulbena A. Updates on the psychological and psychiatric aspects of the Ehlers-Danlos syndromes and hypermobility spectrum disorders. Am. J. Med. Genet. C Semin. Med. Genet. 2021; 187(4): 482-90.

[12] Meester JAN, Verstraeten A, Schepers D, Alaerts M, Van Laer L, Loeys BL. Differences in manifestations of Marfan syndrome, Ehlers-Danlos syndrome, and Loeys-Dietz syndrome. Ann. Cardiothorac. Surg. 2017; 6(6): 582-94.

[13] Malek S, Reinhold EJ, Pearce GS. The Beighton Score as a measure of generalised joint hypermobility. Rheumatol. Int. 2021; 41(10): 1707-16.

[14] Juul-Kristensen B, Schmedling K, Rombaut L, Lund H, Engelbert RH. Measurement properties of clinical assessment methods for classifying generalized joint hypermobility-A systematic review. Am. J. Med. Genet. C Semin. Med. Genet. 2017; 175(1): 116-47.

[15] The Ehlers-Danlos Society. The HEDGE Study – A Global First. 2025 Update [Internet]. 2025 [cited 2025 Dec 11]. Available from: https://www.ehlers-danlos.com/hedge-study-update/

[16] Hakim A. Hypermobile Ehlers-Danlos Syndrome. 2004 Oct 22 [Updated 2024 Feb 22]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews®. Seattle (WA): University of Washington, Seattle; 1993–2025.

[17] Foehr RM, Foehr ED. Vascular Ehlers-Danlos Syndrome: Current

Understanding and Treatment Strategies. J. Rare Dis. Res. Treat. 2025; 9(1): 1–4.

[18] Jones E, Carrieri D. Understanding the issues of hypermobility spectrum disorders and hypermobile Ehlers-Danlos syndrome in primary care: a qualitative integrative review. Disabil. Rehabil. 2025: 1-16.

[19] Hakim AJ, Tofts L. Clinical manifestations and diagnosis of hypermobile Ehlers-Danlos syndrome and hypermobility spectrum disorder. UpToDate. Waltham (MA): Wolters Kluwer; 2021.

[20] Yew KS, Kamps-Schmitt KA, Borge R. Hypermobile Ehlers-Danlos Syndrome and Hypermobility Spectrum Disorders. Am. Fam. Physician. 2021; 103(8): 481–92.

[21] Cooper DJ, Scammell BE, Batt ME, Palmer D. Development and validation of self-reported line drawings of the modified Beighton score for the assessment of generalised joint hypermobility. BMC. Med. Res. Methodol. 2018; 18(1): 11.

[22] Groeneveld Larraz L, Ferrer Benito A, Fuertes Gimeno S, García Pérez A, Esteban Aldana M, Martín Aragón S. Síndrome de Ehlers-Danlos hipermóvil. Artículo monográfico. Rev. Sanitaria Investig. 2024;5(8):381.

[23] Teran-Wodzinski P, Kumar A. Clinical characteristics of patients with hypermobile type Ehlers-Danlos syndrome (hEDS) and generalized hypermobility spectrum disorders (G-HSD): an online survey. Rheumatol. Int. 2023; 43(10): 1935-45.

[24] Monaco A, Choi D, Uzun S, Maitland A, Riley B. Association of mast-cell-related conditions with hypermobile syndromes: a review of the literature. Immunol. Res. 2022; 70(4): 419-31.

[25] Weinstock LB. Mast Cell Activation Syndrome and the Triad of MCAS, POTS, and Hypermobile EDS. Am. J. Gastroenterol. 2024; 120(7): 1429-33.

[26] McClave SA, Gualdoni J, Nagengast A, Marsano LS, Bandy K, Martindale RG. Gastrointestinal Dysfunction and Feeding Intolerance in Critical Illness: Do We Need an Objective Scoring System? Curr. Gastroenterol. Rep. 2020; 22(1): 1.

[27] Ishiguro H, Yagasaki H, Horiuchi Y. Ehlers-Danlos Syndrome in the Field of Psychiatry: A Review. Front. Psychiatry. 2022; 12:803898.

[28] Hershenfeld SA, Wasim S, McNiven V, Parikh M, Majewski P, Faghfoury H, et al. Psychiatric disorders in Ehlers-Danlos syndrome are frequent, diverse and strongly associated with pain. Rheumatol. Int. 2016; 36(3): 341-8.

[29] Fletcher EKS, Fischer AL, Manocha RHK. Depressive symptoms are highly prevalent and associated with fatigue and pain catastrophizing in the Hypermobility Spectrum Disorders and hypermobile Ehlers Danlos syndrome: a cross-sectional study. Rheumatol. Int. 2025: 45(5): 128.

[30] Schubert-Hjalmarsson E, Öhman A, Kyllerman M, Beckung E. Pain, balance, activity, and participation in children with hypermobility syndrome. Pediatr. Phys Ther. 2012; 24(4): 339–44.

[31] Clark NL, Johnson M, Rangan A, Kottam L, Swainston K, McLean SM. The biopsychosocial impact of hypermobility spectrum disorders in adults: a scoping review. Rheumatol. Int. 2023; 43: 985–1014.

[32] Bozkaya OG, Cinleti T. Ehlers-Danlos Syndrome: Primary Care Clinical Guidelines for Diagnosis and Disease Management. Ann. Pediatr. 2023; 6(2): 1126.

[33] Atwell K, Michael W, Dubey J, James S, Martonffy A, Anderson S, et al. Diagnosis and Management of Hypermobility Spectrum Disorders in Primary Care. J. Am. Board Fam. Med. 2021; 34(4):838-48.

[34] Russek LN, Stott P, Simmonds J. Recognizing and Effectively Managing Hypermobility-Related Conditions. Phys. Ther. 2019; 99(9):1189-200.

[35] Black WR, Black LL, Goldstein-Leever A, Fox LS, Pratt LR, Jones JT. The need for primary care providers in the clinical management of hypermobility spectrum disorders and ehlers-danlos syndrome: a call to action. Rheumatol. Int. 2024; 44(11): 2273-8