Hypermobile Ehlers-Danlos Syndrome and Hypermobility Spectrum Disorders

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Hypermobile Ehlers-Danlos syndrome (EDS) and hypermobility spectrum disorders are the most common symptomatic joint hypermobility conditions seen in clinical practice. The 2017 International Classification of the Ehlers-Danlos syndromes replaced previous terms for symptomatic joint hypermobility with hypermobile EDS and introduced the term hypermobility spectrum disorders for patients not meeting diagnostic criteria for hypermobile EDS. Both are diagnosed by applying the 2017 diagnostic criteria, which also excludes other less common conditions presenting with joint hypermobility such as other forms of EDS and heritable connective tissue disorders. Hypermobile EDS is inherited in an autosomal dominant pattern, but it does not have a known genetic mutation to help with diagnosis. Clinical features of hypermobile EDS include joint hypermobility, skin findings, and joint pains or recurrent dislocations. Hypermobile EDS and, less commonly, hypermobility spectrum disorders may also be associated with several extra-articular symptoms, including anxiety disorders, chronic pain, fatigue, orthostatic intolerance, functional gastrointestinal disorders, and pelvic and bladder dysfunction. The central goals of therapy are managing symptoms, preventing joint injury, and educating patients about their condition. Based on limited evidence, patients with hypermobile EDS/hypermobility spectrum disorders may benefit from physical and occupational therapy, psychological support, and self-management. Primary care physicians play a key role not only in initial recognition, diagnosis, and patient education, but by virtue of their ongoing relationship they can also help oversee and coordinate the multidisciplinary team many of these patients require. (*Am Fam Physician*. 2021;103(8):481-492. Copyright © 2021 American Academy of Family Physicians.)

Hypermobile Ehlers-Danlos syndrome (EDS) and hypermobility spectrum disorders are the most common symptomatic joint hypermobility conditions seen in clinical practice.[1,2] Family physicians play a vital role in the care of patients with these conditions, from initial diagnosis to ongoing care.

Definitions

"Ehlers-Danlos syndromes (EDS) … are a group of inherited connective tissue disorders caused by abnormalities in the structure, production, and/or processing of collagen. The new classification, from 2017, includes 13 subtypes of EDS."[3] *Table 1* describes these subtypes.[1,4,5] Joint hypermobility is a feature common among many EDS subtypes and other heritable connective tissue disorders. Joint hypermobility is defined as the ability of a joint to move "beyond normal limits along physiological axes."[4] Joint hypermobility can involve a few or many joints and may be entirely

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WHAT'S NEW ON THIS TOPIC

Hypermobility Spectrum Disorders

The 2017 International Classification of the Ehlers-Danlos syndromes replaced prior terms for symptomatic joint hypermobility with hypermobile Ehlers-Danlos syndrome and introduced the term hypermobility spectrum disorder for patients not meeting hypermobile Ehlers-Danlos syndrome diagnostic criteria.

A 2013 U.K. population survey found that 3.4% of adults endorsed hypermobility and chronic widespread pain using validated instruments.

Generalized joint hypermobility is more common than hypermobile Ehlers-Danlos syndrome/hypermobility spectrum disorders because patients with generalized joint hypermobility may be asymptomatic. When assessed in student population samples using the 2017 criteria, 4% to 11% of children three to 19 years of age had generalized joint hypermobility.

TABLE 1

Overlap between Joint Hypermobility, Hypermobility Spectrum Disorders, and Ehlers-Danlos Syndromes

Type	Beighton score	Musculoskeletal involvement*	Notes
Asymptomatic joint hypermobility			
Asymptomatic generalized joint hypermobility	Positive	Absent	—
Asymptomatic peripheral joint hypermobility	Usually negative	Absent	Joint hypermobility typically limited to hands and/or feet
Asymptomatic localized joint hypermobility	Negative	Absent	Joint hypermobility limited to single joint or body parts
Hypermobility spectrum disorders			
Generalized hypermobility spectrum disorders	Positive	Present	Does NOT meet criteria for hypermobile EDS based on limited findings in skin and musculoskeletal systems and lack of family history No genes identified Screening with echocardiography unnecessary
Peripheral hypermobility spectrum disorders	Usually negative	Present	Joint hypermobility typically limited to hands and/or feet
Localized hypermobility spectrum disorders	Negative	Present	Joint hypermobility limited to single joints or body parts
Historical hypermobility spectrum disorders	Negative	Present	Historical presence of joint hypermobility
EDS – Joint hypermobility with more pronounced skin and musculoskeletal findings and/or positive family history			
1. Hypermobile EDS	Positive	Possible	Meet criteria based on supportive findings in skin and body systems and/or positive family history (see Figure 2) No genes identified AD inheritance pattern Obtain screening echocardiography

Type	Beighton score	Major features	Gene affected
EDS			
2. Classical	Positive	Skin hyperextensibility Abnormal scarring	*COL5A1*, *COL5A2* genes Rare *COL1A1* gene AD inheritance
3. Classical-like	Positive	Skin hyperextensibility Easy bruising	*TNXB* gene AR inheritance
4. Cardiac-valvular	Positive or negative, general hypermobility or restricted to small joints	Cardiac valvular problems Skin involvement	*COL1A2* gene AR inheritance
5. Vascular	Positive or negative	Family history of vascular EDS History of early arterial rupture or uterine rupture, sigmoid colon perforation, or atraumatic carotid-cavernous sinus fistula formation	*COL3A1* gene Rare *COL1A1* gene AD inheritance

continues

AD = autosomal dominant; AR = autosomal recessive; EDS = Ehlers-Danlos syndrome.

*—Musculoskeletal involvement includes the following: (1) pain; (2) musculoskeletal/soft tissue trauma, including dislocations, subluxations, soft tissue damage, and microtraumas (microtraumas include small tears of muscles, sprained ligaments, strained muscles, and overstretched tendons); (3) disturbed proprioception; and (4) other musculoskeletal conditions (e.g., flexible flat feet; valgus abnormality of the elbow, hindfoot, and hallux; kyphosis; scoliosis; deformational plagiocephaly).

TABLE 1 *(continued)*

Overlap between Joint Hypermobility, Hypermobility Spectrum Disorders, and Ehlers-Danlos Syndromes

Type	Beighton score	Major features	Gene affected
EDS *(continued)*			
6. Arthrochalasia	Positive	Congenital bilateral hip dislocation Skin hyperextensibility	*COL1A1*, *COL1A2* genes AD inheritance
7. Dermatosparaxis	Positive or negative	Extreme skin fragility Characteristic craniofacial features	*ADAMTS2* gene AR inheritance
8. Kyphoscoliotic	Positive with history of dislocation and subluxation	Congenital hypotonia Kyphoscoliosis	*PLOD1*, *FKBP14* genes AR inheritance
9. Brittle cornea syndrome	Positive or negative	Thin cornea with or without rupture Keratoconus Keratoglobus Blue sclerae	*ZNF469*, *PRDM5* genes AR inheritance
10. Spondylodysplastic	Positive or negative	Short stature Muscle hypotonia Bowing of limbs	*B4GALT7*, *B3GALT6*, *SLC39A13* genes AR inheritance
11. Musculocontractural	Positive or negative	Congenital multiple contractures Characteristic craniofacial features Skin involvement	*CHST14*, *DSE* genes AR inheritance
12. Myopathic	Distal joints affected	Congenital muscle hypotonia and/or atrophy that improves with age Proximal muscle contractures	*COL12A1* gene AD or AR inheritance
13. Periodontal	Positive or negative	Periodontitis Lack of attached gingiva Pretibial plaques Family history of periodontal EDS	*C1R*, *C1S* genes AD inheritance

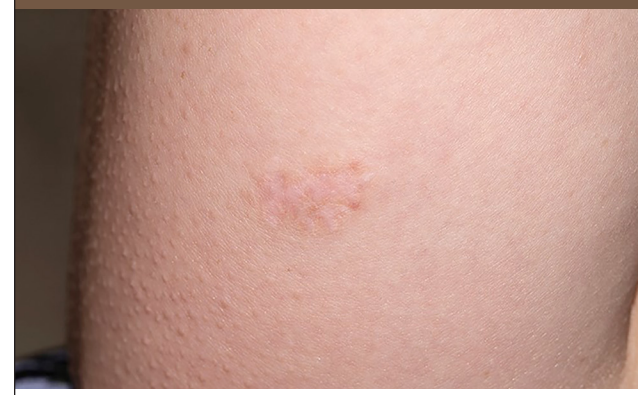
AD = autosomal dominant; AR = autosomal recessive; EDS = Ehlers-Danlos syndrome.

Information from references 1, 4, and 5, and personal communication from Karyn Laursen, MD.

asymptomatic. Generalized joint hypermobility is more likely to be associated with a genetic syndrome than localized joint hypermobility. The exception is hypermobile EDS, which is the most common EDS variant, representing 80% to 90% of EDS cases,[2] with clinical features including joint hypermobility, skin findings *(Figure 1)*, and joint pains or recurrent dislocations *(Figure 2*[6] and *Figure 3*[1,7]*)*. The 2017 classification introduced stricter criteria for hypermobile EDS than previously available to distinguish patients with hypermobile EDS from those most likely to have a diagnosable genetic syndrome.[1] For patients with symptomatic joint hypermobility satisfying neither the new hypermobile EDS criteria nor another specific condition, the 2017 classification introduced hypermobility spectrum disorders.[1]

Patients with hypermobility spectrum disorders are distinct from those with hypermobile EDS and other syndromes with joint hypermobility in that their symptoms are

FIGURE 1



Atrophic scar.

FIGURE 2

The International Consortium on Ehlers-Danlos Syndromes & Related Disorders
In Association with The Ehlers-Danlos Society

Diagnostic Criteria for Hypermobile Ehlers-Danlos Syndrome (hEDS)

This diagnostic checklist is for doctors across all disciplines to be able to diagnose EDS

Distributed by The Ehlers Danlos Society.

Patient name: _____ Date of birth: _____ Date of visit: _____ Evaluator: _____

For clinical diagnosis of hypermobile EDS, criteria 1 *and* 2 *and* 3 must be present simultaneously

Criterion 1: generalized joint hypermobility

☐ Beighton score: _____/9 (see Table 5)

One of the following selected:

☐ Beighton score ≥ 6 in prepubertal children and adolescents

☐ Beighton score ≥ 5 from puberty up to 50 years of age

☐ Beighton score ≥ 4 in persons older than 50 years

If Beighton score is one point below age- and sex-specific cutoff, two or more of the following must also be selected to meet criterion 1:

☐ Can you now (or could you ever) place your hands flat on the floor without bending your knees?

☐ Can you now (or could you ever) bend your thumb to touch your forearm?

☐ As a child, did you amuse your friends by contorting your body into strange shapes or could you do the splits?

☐ As a child or teenager, did your shoulder or kneecap dislocate on more than one occasion?

☐ Do you consider yourself double-jointed?

Criterion 2: two or more of the following features (A, B, or C) must be present

Feature A *(five of the following must be present)*

☐ Unusually soft or velvety skin

☐ Mild skin hyperextensibility

☐ Unexplained striae distensae or rubrae at the back, groin, thighs, breasts, and/or abdomen in adolescents, men, or prepubertal girls without a history of significant gain or loss of body fat or weight

☐ Bilateral piezogenic papules of the heel

☐ Recurrent or multiple abdominal hernias

☐ Atrophic scarring involving at least two sites and without the formation of truly papyraceous and/or hemosideric scars as seen in classical EDS

☐ Pelvic floor, rectal, and/or uterine prolapse in children, men, or nulliparous women without a history of morbid obesity or other known predisposing medical condition

☐ Dental crowding and high or narrow palate

☐ Arachnodactyly, as defined in one or more of the following: (1) positive wrist sign (Walker sign) on both sides or (2) positive thumb sign (Steinberg sign) on both sides

☐ Ratio of arm span to height ≥ 1.05

☐ Mitral valve prolapse mild or greater based on strict echocardiography criteria

☐ Aortic root dilation with Z-score > +2

☐ Feature A total: _____/12

Feature B

☐ Positive family history: one or more first-degree relatives independently meeting the current criteria for hypermobile EDS

Feature C *(must have at least one)*

☐ Musculoskeletal pain in two or more limbs, recurring daily for ≥ 3 months

☐ Chronic, widespread pain for ≥ 3 months

☐ Recurrent joint dislocations or frank joint instability in the absence of trauma

Criterion 3: all of the following prerequisites MUST be met

☐ 1. Absence of unusual skin fragility, which should prompt consideration of other types of EDS

☐ 2. Exclusion of other heritable and acquired connective tissue disorders, including autoimmune rheumatologic conditions. In patients with an acquired connective tissue disorder (e.g., lupus, rheumatoid arthritis), additional diagnosis of hypermobile EDS requires meeting both features A and B of criterion 2. Feature C of criterion 2 (chronic pain and/or instability) cannot be counted toward a diagnosis of hypermobile EDS in this situation.

☐ 3. Exclusion of alternative diagnoses that may also include joint hypermobility by means of hypotonia and/or connective tissue laxity. Alternative diagnoses and diagnostic categories include, but are not limited to, neuromuscular disorders (e.g., Bethlem myopathy), other hereditary disorders of the connective tissue (e.g., other types of EDS, Loeys-Dietz syndrome, Marfan syndrome), and skeletal dysplasias (e.g., osteogenesis imperfecta). Exclusion of these considerations may be based on history, physical examination, and/or molecular genetic testing, as indicated.

Diagnosis: _____

_____

_____

EDS = Ehlers-Danlos syndrome.

Diagnostic criteria for hypermobile EDS.

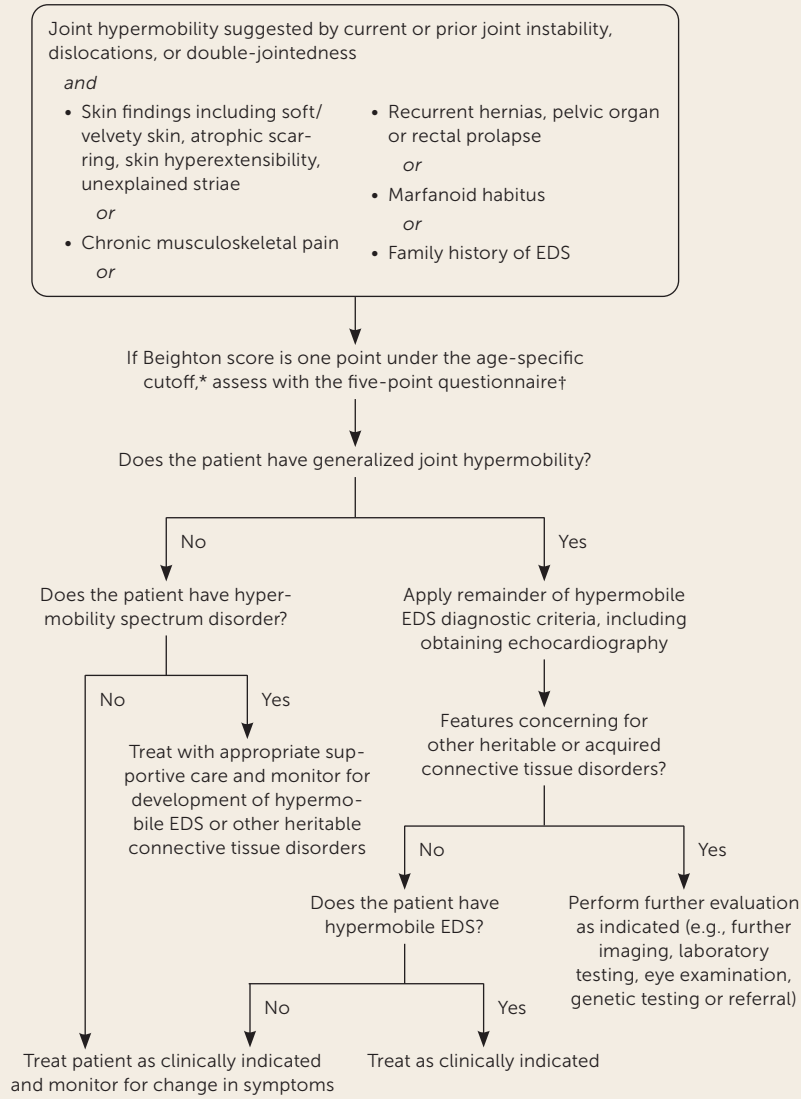
Adapted with permission from The International Consortium on Ehlers-Danlos Syndromes & Related Disorders in association with the Ehlers-Danlos Society. Diagnostic criteria for hypermobile Ehlers-Danlos syndrome. Accessed March 2, 2020. https://www.ehlers-danlos.com/wp-content/uploads/hEDS-Dx-Criteria-checklist-1.pdf

primarily musculoskeletal; however, limited extra-articular involvement may be seen.[4] All previous terms, including EDS type III, EDS hypermobility type, hypermobility syndrome, joint hypermobility syndrome, and benign joint hypermobility syndrome, should no longer be used.[4] At one time, these earlier named diagnoses were thought to represent distinct entities, but subsequent studies finding broad overlap of these older named conditions within families demonstrated that they were the same entity.[4] In a more recent study, nearly all patients with one of the earlier, now outdated, diagnoses fulfilled either hypermobile EDS or hypermobility spectrum disorders criteria.[8] Because they are the most common symptomatic hypermobility conditions, their evaluation and management are the focus of this article; the terms hypermobile EDS and hypermobility spectrum disorders will be used except when clarity dictates reference to an older diagnostic term.

Epidemiology and Pathogenesis

The exact prevalence of hypermobile EDS/hypermobility spectrum disorders is unknown. The best estimates of the population prevalence of these conditions are derived from studies in national or patient registries from Sweden and Wales, United Kingdom, using diagnostic codes for EDS and joint hypermobility syndrome, the latter a prior term for hypermobile EDS, as discussed previously.[9,10] The combined hypermobile EDS/hypermobility spectrum disorders prevalence would be expected to be lower than the 0.13% to 0.19% prevalence that these two studies found for all EDS and joint hypermobility syndrome codes combined.[9,10] This prevalence equates to about seven to 10 patients out of a 5,000-patient panel. Another estimate of combined

FIGURE 3



EDS = Ehlers-Danlos syndrome.

Diagnostic approach to a patient with possible hypermobile EDS.

Information from references 1 and 7.

hypermobile EDS/hypermobility spectrum disorders prevalence from a U.K. population survey found that 3.4% of adults endorsed hypermobility and chronic widespread pain using validated instruments.[11]

Generalized joint hypermobility, a diagnostic criterion for hypermobile EDS, is more common than hypermobile EDS/hypermobility spectrum disorders because patients with generalized joint hypermobility may be asymptomatic. When assessed in student population samples using 2017 criteria, 4% to 11% of children three to 19 years of age had generalized joint hypermobility.[12-17] The percentage of people with generalized joint hypermobility who are eventually diagnosed with hypermobile EDS/hypermobility spectrum disorders is unknown.

Hypermobile EDS is the only EDS subtype for which a genetic mutation has not been discovered. Hypermobile EDS is considered to be inherited in an autosomal dominant manner with incomplete penetrance. The pathogenesis of hypermobile EDS and hypermobility spectrum disorders is still being unraveled but involves muscle and tendon laxity,[18] reduced proprioception,[19] significantly disordered connective tissue structure, and alterations in gene expression.[20]

Clinical Presentation

Hypermobile EDS and hypermobility spectrum disorders exhibit a complex range of signs and symptoms of varying degrees and combinations that make these conditions difficult to recognize. Common presenting features of hypermobile EDS are listed in *Table 2*.[1,2,21] The prevalence of generalized joint hypermobility declines with age,[2] and this decline is considered by the 2017 hypermobile EDS criteria by incorporating historical questions for patients with subthreshold joint hypermobility.[1,7] The strongest systemic findings associated with hypermobile EDS include anxiety disorders, chronic pain, fatigue, orthostatic intolerance, functional gastrointestinal disorders, and pelvic and bladder dysfunction.[22-26] *Table 3* describes the symptoms and physical findings commonly associated with hypermobile EDS.[2,22,23,26-38]

Diagnostic Evaluation

CLINICAL FEATURES

The diagnosis of hypermobile EDS should be considered in patients with clinical features noted in *Table 2*.[1,2,21] Patients with systemic manifestations *(Table 3*[2,22,23,26-38]*)* and a history of joint hypermobility or arthralgias also may have hypermobile EDS or a related disorder that was overlooked or previously misdiagnosed.[1] A U.K. patient survey found the median time to diagnosis was 10 years.[39]

The diagnosis of hypermobile EDS/hypermobility spectrum disorders is made by medical history, physical examination, and exclusion of other conditions that present with musculoskeletal hypermobility.[2,40,41] Diagnostic criteria for hypermobile EDS are listed in *Figure 2*.[6] *Table 1* outlines criteria for hypermobility spectrum disorders when patients meet neither criteria for hypermobile EDS nor another specific condition.[1,4,5] A differential diagnosis for joint hypermobility appears in *Table 4*.[1,4,21,42] Taking a careful family history that inquires about joint hypermobility, musculoskeletal symptoms, aneurysms, and genetic conditions is essential. Once hypermobile EDS is suspected, the physician should determine the degree

TABLE 2

Common Presenting Features of Hypermobile Ehlers-Danlos Syndrome

Feature	Comment
History*	
Clumsiness, motor or speech delay in childhood	Particularly with family history of Ehlers-Danlos syndrome
Extreme flexibility or double-jointed	Older adults may recall being double-jointed or extremely flexible in childhood
Recurrent or chronic joint pains	May be limited or widespread
Joint subluxation or dislocations without significant trauma	Shoulder, knee, and hip most commonly affected
Recurrent hernias, pelvic organ prolapse, or rectal prolapse	Especially when no other known predisposing condition present
Physical finding	
Marfanoid habitus	May be present in up to one-third of patients[21]
Skin findings	Skin hyperextensibility > 1.5 cm on midvolar forearm of nondominant arm[1]
Unusually soft, silky, or velvety skin	
Mildly hyperextensible skin	Scars may be wider or more shallow than normal[1]
Mild scar atrophy (Figure 1)	
Striae distensae or rubrae	Striae often appear in adolescence unassociated with weight gain or pregnancy[1]
Piezogenic papules: small subcutaneous fat herniations at lateral heels[1]	

*—Features may occur sequentially.

Information from references 1, 2, and 21.

TABLE 3

Symptoms Associated with Hypermobile Ehlers-Danlos Syndrome

Organ system	Symptoms/physical findings
Autonomic[27,28]	Neurally mediated hypotension/syncope
	Orthostatic intolerance
	Postural orthostatic tachycardia syndrome
Cardiovascular[29]	Low progressive aortic root dilation
	Mitral valve prolapse/insufficiency
Gastrointestinal[22]	Chronic/recurrent gastritis
	Defecatory dysfunction
	Delayed gastric emptying
	Delayed small bowel and colonic transit
	Dysphagia
	Dysphonia
	Gastroesophageal reflux
	Hiatal hernia
	Unexplained abdominal pain
	Various food intolerances
	Visceroptosis (prolapse of the abdominal viscera)
Gynecologic[26,30]	Disabling dysmenorrhea
	Dyspareunia
	Menorrhagia/metrorrhagia
	Pelvic organ prolapse
	Urinary stress incontinence
Mucocutaneous[31]	Atrophic scars
	Easy bruising
	Gingival inflammation/recessions
	Hernias (inguinal/umbilical/incisional)
	Hypoplastic lingual frenulum
	Keratosis pilaris
	Light blue sclerae
	Mildly hyperextensible skin
	Resistance to local anesthetic drugs
	Velvety/silky/soft skin texture
Musculoskeletal[2,32-34]	Chronic pain
	Chronic/recurrent noninflammatory joint pain
	Early osteoarthritis
	Fibromyalgia
	Flatfoot
	Generalized joint hypermobility
	High arched/narrow palate
	Involuntary muscle contractions
	Marfanoid habitus (ratio of arm span to height > 1.05)
	Mild scoliosis, dorsal hyperkyphosis, lumbar hyperlordosis
	Myofascial pain
	Nonpostmenopausal reduced bone mass
	Nonsurgical pectus excavatum
	Recurrent dislocations (e.g., hips, shoulders, temporomandibular, fingers)
	Recurrent myalgias and cramps
	Recurrent soft tissue lesions
	Temporomandibular joint dysfunction
Neurologic[32,34,35]	Clumsiness
	Headache and migraines
	Impaired memory and concentration
	Sleep disturbances
	Somatosensory/central sensitization
Ocular[36]	Myopia and/or strabismus
	Palpebral ptosis
Psychological[23,37,38]	Attention-deficit/hyperactivity disorder
	Chronic fatigue/chronic fatigue syndrome
	Depression
	Generalized anxiety
	Obsessive-compulsive disorder
	Panic attacks
	Phobias, kinesiophobia

Information from references 2, 22, 23, and 26-38.

and pattern of hypermobility using a validated tool known as the Beighton score[1,40,41,43] *(Table 5*[1,44]*)*. The Beighton score incorporates five maneuvers to calculate a score between 0 and 9. The 2017 hypermobile EDS criteria in *Figure 2* specify that if the Beighton score is one point below age-specific and sex-specific cutoffs for generalized joint hypermobility, the next step is to administer a validated five-part questionnaire to help determine whether the patient has generalized joint hypermobility, a necessary criterion for the diagnosis of hypermobile EDS.[6,7] Patients without generalized joint hypermobility may still have hypermobility spectrum disorders. *Figure 3* suggests an evaluation strategy for patients suspected of having hypermobile EDS or hypermobility spectrum disorders.[1,7]

If generalized joint hypermobility is confirmed in patients with suspected hypermobile EDS, the remainder of the hypermobile EDS criteria are sought[1] *(Figure 2*[6]*)*. This involves asking the patient about a history of musculoskeletal symptoms, abdominal hernias, and organ and mitral valve prolapse; examining the skin; testing for arachnodactyly; and measuring the ratio of arm span to height. *Figure 1* shows a typical atrophic scar.

DIAGNOSTIC TESTING

No confirmatory test exists, so hypermobile EDS and hypermobility spectrum disorders remain clinical diagnoses.[2] Laboratory testing and radiography to evaluate for acquired connective tissue disorder or suspected bone or joint injury are guided by clinical history and physical examination. The presence of marfanoid features requires distinguishing between hypermobile EDS and Marfan-related syndromes. *Table 4* lists features that can help to distinguish between these conditions.[1,4,21,42] Screening echocardiography should be performed to evaluate for aortic root dilation or mitral valve prolapse in patients with possible hypermobile EDS. Specific genetic testing should be performed for other EDS variants, Marfan and Loeys-Dietz syndromes, and other genetic conditions when suspected *(Table 4)*.[1,4,21,42] It often takes several visits to complete a diagnostic evaluation. Many patients who do not meet hypermobile EDS criteria and do not have clear evidence for another specific syndrome will meet criteria for hypermobility spectrum disorders. If the diagnosis remains unclear, referral to a genetics specialist for further evaluation may be required. *eTable A* lists resources supporting the diagnosis and management of hypermobility syndromes.

Management

The central goals of therapy are managing symptoms, preventing joint injury, and teaching patients about their condition.[45-48] Based on limited evidence and expert opinion, the mainstays of management for hypermobile EDS and hypermobility spectrum disorders include patient education, physical and occupational therapy, psychological support, and self-management. Symptoms of hypermobility spectrum disorders may resolve with therapy, persist, or progress to hypermobile EDS. Hypermobile EDS is managed as a lifelong condition because no curative treatments currently exist.

Treatment strategies are diverse because of the many different systems that may be involved. Patients with hypermobile EDS can benefit from a multidisciplinary team that includes physicians, nursing staff, physical therapists,

TABLE 4

Selected Differential Diagnosis of Joint Hypermobility

Condition	Distinguishing features
Acquired conditions including diffuse degenerative disorders of muscles, joints, or nerves; hypothyroidism; or malnutrition	Suggestive medical history
Chromosomal and genomic disorders including Down syndrome, aneuploidies (47, XXY; 47, XXX), and several microdeletion and microduplication syndromes	Dysmorphic features Hypogonadism
Hereditary cutis laxa[42]: multiple subtypes	Loose, inelastic skin
Hereditary myopathies: Bethlem, Ullrich, and others	Hypotonia and weakness Joint hyperlaxity and contractures
Loeys-Dietz syndrome	Arterial tortuosity and aortic aneurysms Cleft palate/bifid uvula Hypertelorism Hypotonia
Marfan syndrome, Beals syndrome, MASS phenotype, and arterial tortuosity syndrome	Ectopia lentis in Marfan syndrome Mitral valve prolapse in MASS phenotype Progressive ascending aortic dilation Tortuous medium and large arteries in arterial tortuosity syndrome
Multiple congenital anomaly or intellectual disability disorders including RASopathies, Kabuki make-up syndrome, and FG syndrome Fragile X syndrome	Multiple congenital anomalies or intellectual disabilities
Other variants of Ehlers-Danlos syndrome including classical, vascular, and rarer forms	Acrogeria* Arterial, viscus, or lung rupture Features specific to rarer types of Ehlers-Danlos syndrome in Table 1 Muscle weakness Pronounced skin hyperextensibility Unusual skin fragility, papyraceous or hemosideric scars
Skeletal dysplasias: osteogenesis imperfecta type I, Larsen syndrome, Desbuquois syndrome, and others	Blue sclerae Bone fragility Neonatal joint dislocations

MASS = mitral valve, myopia, aorta, skin, and skeletal features of the disorder.

*—Acrogeria: thin, atrophied skin and subcutaneous fat in the hands and feet giving the appearance of accelerated aging that may be seen in vascular Ehlers-Danlos syndrome.

Information from references 1, 4, 21, and 42.

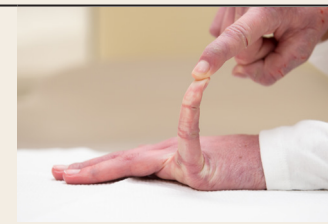
occupational therapists, orthotists, nutritionists and/or lifestyle coaches, psychologists, and community and online support. Specialty care can help in the management of skin, joint, cardiovascular, and gastrointestinal complications and chronic pain. Family physicians play a key role in overseeing and coordinating the complex care that many patients with hypermobile EDS require.

Management of musculoskeletal complaints includes conservative treatments such as physical activity, acetaminophen and nonsteroidal anti-inflammatory drugs, heat and/or cold application, improved ergonomics and posture, relaxation techniques, massage, hydrotherapy, and joint stabilization techniques with bracing and/or taping.[47,49,50] Medications that diminish platelet function should generally be avoided in patients with hypermobile EDS who have easy bruising. Physical therapists should customize their education on strengthening exercises, proprioceptive exercises, and joint protection.[51] Occupational therapists can help strengthen upper extremity and hand muscles, improve activities of daily living, and introduce patients to adaptive writing instruments and other adaptive tools. Tai chi has shown benefit in patients with osteoarthritis, fibromyalgia, and low back pain,[52] although it has not been studied in those who have hypermobile EDS/hypermobility spectrum disorders. The use of splints and orthotics can help selected patients.

Educating patients about lifestyle modifications, management options, and expectations is one of the most important interventions. Encouraging the optimization of sleep, joint protection through the proper amount of regular physical exercise (low impact and low resistance), weight control, avoidance of substance use (e.g., alcohol, nicotine), and the consumption of a healthy diet can decrease pain,

TABLE 5

Beighton Hypermobility Score

Maneuver	Image	Right side scoring	Left side scoring
Ability to passively dorsiflex the fifth metacarpophalangeal joint ≥ 90 degrees		___ / 1 point	___ / 1 point
Ability to oppose the thumb to the volar aspect of the ipsilateral forearm		___ / 1 point	___ / 1 point
Ability to hyperextend the elbow joint > 10 degrees		___ / 1 point	___ / 1 point
Ability to hyperextend the knee joint > 10 degrees		___ / 1 point	___ / 1 point
Ability to place hands flat on the floor by bending forward with knees fully extended		___ / 1 point	
		Total	___ / 9 points

Note: The Beighton score is the summed total of the scores from each extremity and bending forward.

Information from references 1 and 44.

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	Evidence rating	Comments
Suspect hypermobile EDS/hypermobility spectrum disorders in patients with joint hypermobility and associated symptoms such as joint pain or dislocations and typical skin findings, arthralgias, recurrent hernias, marfanoid habitus, or family history of EDS.[1]	C	Expert opinion from 2017 International Classification of the Ehlers-Danlos syndromes
Assess joint hypermobility in patients suspected of having hypermobile EDS/hypermobility spectrum disorders with a Beighton score and a validated five-part questionnaire.[1,41,43]	C	Disease-oriented outcomes and expert opinion
Early multidisciplinary treatment that includes physical, occupational, and cognitive behavior therapy; orthotics; and community and specialty support may optimize outcomes in patients with joint hypermobility symptoms.[46-48,58,59]	C	Expert opinion and several case series studies

EDS = Ehlers-Danlos syndrome.

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to https://www.aafp.org/afpsort.

injuries, and fatigue and support mobility and functionality. Orthostatic intolerance can be lessened by increasing fluids, increasing salt intake, and using compression stockings.

Qualitative studies describe the experience of patients who have pain and disability with hypermobile EDS that is frequently minimized or invalidated in their social circles, and even in medical settings, because the patients are perceived as looking "normal" or the condition is not recognized.[53-55] The complexity of hypermobile EDS/hypermobility spectrum disorders and the lack of familiarity physicians may have can lead them to ignore or be skeptical of patients' experiences with their EDS conditions, possibly having lasting negative impacts on patients.[56] Qualitative data strongly support the notion that earlier diagnosis and empathetic, knowledgeable clinical care are highly desired by patients,[53-55] but further research is needed to confirm whether earlier diagnosis and skilled, caring support improve outcomes beyond patient satisfaction. The risks and benefits of invasive testing and procedures must be reviewed carefully in patients with all forms of EDS because bleeding complications, inadequate response to regional and local anesthesia, and iatrogenic injury are common.[57]

Finally, physicians should be aware of and empathetic toward the cognitive deficits, negative emotions, and alterations in activity that can complicate this challenging condition.[37] More research is needed, but three small studies of a multidisciplinary approach that includes physical, occupational, and cognitive behavior therapy have shown reduced anxiety, depression, catastrophizing, and kinesiophobia (fear of pain due to movement), with improved physical function and self-efficacy in treated patients.[32,58,59] A similar multidisciplinary intervention that lacked cognitive behavior therapy showed no benefit.[45]

Prognosis

A three-phase natural history of hypermobile EDS has been proposed based on a large Italian case series.[49] In this series, patients progressed from generalized joint hypermobility alone with or without joint pain in childhood to having musculoskeletal pain, falls, mixed headache, and functional gastrointestinal disorders by the second and third decades of life. By the third to fourth decades of life, patients developed inflexibility, widespread pain, and limiting fatigue. The prognosis of hypermobile EDS/hypermobility spectrum disorders varies widely and is difficult to predict for individual patients. A convenience sample of children diagnosed with a precursor to hypermobile EDS at a tertiary hospital who were followed for three years found four factors that predicted disease severity and modestly predicted development of disability over time: multisystem involvement, pain, fatigue, and postural control.[60] However, variable outcomes were the rule. In adults, chronic pain, gastrointestinal and genitourinary problems, fatigue, restricted mobility, and frequent injuries were most often associated with the functional outcomes of decreased perceived quality of life and decreased participation in activities of daily living.[30,53,61]

Data Sources: Search in MEDLINE and CINAHL for joint hypermobility (in general, including EDS) and epidemiolog$.mp, risk factors, (pathogenesis or pathogenetic or pathogenic$ or pathogeny).mp, clinical presentation, symptoms, diagnosis, diagnostic criteria, clinical management or prognosis limiting to English and the past 10 years with additional review of bibliographies for relevant articles. *American Family Physician* editors

identified no relevant evidence from POEMs or the Cochrane database. No relevant guidelines were found in the ECRI Guidelines Trust or the U.S. Preventive Services Task Force. Search dates: November 25 and 26, 2019; and October 28, 2020.

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