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.)

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

<table>
<thead>
<tr>
<th>Type</th>
<th>Beighton score</th>
<th>Musculoskeletal involvement*</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic joint hypermobility</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic generalized joint hypermobility</td>
<td>Positive</td>
<td>Absent</td>
<td>—</td>
</tr>
<tr>
<td>Asymptomatic peripheral joint hypermobility</td>
<td>Usually negative</td>
<td>Absent</td>
<td>Joint hypermobility typically limited to hands and/or feet</td>
</tr>
<tr>
<td>Asymptomatic localized joint hypermobility</td>
<td>Negative</td>
<td>Absent</td>
<td>Joint hypermobility limited to single joint or body parts</td>
</tr>
<tr>
<td>Hypermobility spectrum disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generalized hypermobility spectrum disorders</td>
<td>Positive</td>
<td>Present</td>
<td>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</td>
</tr>
<tr>
<td>Peripheral hypermobility spectrum disorders</td>
<td>Usually negative</td>
<td>Present</td>
<td>Joint hypermobility typically limited to hands and/or feet</td>
</tr>
<tr>
<td>Localized hypermobility spectrum disorders</td>
<td>Negative</td>
<td>Present</td>
<td>Joint hypermobility limited to single joints or body parts</td>
</tr>
<tr>
<td>Historical hypermobility spectrum disorders</td>
<td>Negative</td>
<td>Present</td>
<td>Historical presence of joint hypermobility</td>
</tr>
<tr>
<td>EDS – Joint hypermobility with more pronounced skin and musculoskeletal findings and/or positive family history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Hypermobile EDS</td>
<td>Positive</td>
<td>Possible</td>
<td>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</td>
</tr>
</tbody>
</table>

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

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).
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, with clinical features including joint hypermobility, skin findings (Figure 1), and joint pains or recurrent dislocations (Figure 2 and Figure 3). 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. For patients with symptomatic joint hypermobility satisfying neither the new hypermobile EDS criteria nor another specific condition, the 2017 classification introduced hypermobility spectrum disorders.

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

### TABLE 1 (continued)

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

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

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

**FIGURE 1**

Atrophic scar.
Diagnostic Criteria for Hypermobile Ehlers-Danlos Syndrome (hEDS)

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

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
  - 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
  - Dental crowding and high or narrow palate
  - Atlantoaxial subluxation

- Feature B

- 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**

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

primarily musculoskeletal; however, limited extra-articular involvement may be seen. 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. 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. 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. 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. 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. This prevalence equates to about seven to 10 patients out of a 5,000-patient panel. Another estimate of combined

FIGURE 3

Joint hypermobility suggested by current or prior joint instability, dislocations, or double-jointedness

- Skin findings including soft/velvety skin, atrophic scarring, skin hyperextensibility, unexplained striae or
- Chronic musculoskeletal pain or
- Recurrent hernias, pelvic organ or rectal prolapse or
- Marfanoid habitus or
- Family history of EDS

If Beighton score is one point under the age-specific cutoff,* assess with the five-point questionnaire†

Does the patient have generalized joint hypermobility?

No

Does the patient have hypermobility spectrum disorder?

No

Treat with appropriate supportive care and monitor for development of hypermobile EDS or other heritable connective tissue disorders

Yes

Features concerning for other heritable or acquired connective tissue disorders?

No

Does the patient have hypermobile EDS?

Yes

Perform further evaluation as indicated (e.g., further imaging, laboratory testing, eye examination, genetic testing or referral)

No

Treat patient as clinically indicated and monitor for change in symptoms

Yes

Treat as clinically indicated

Criteria for generalized joint hypermobility*

1. Beighton score ≥ 6 in prepubertal children and adolescents
2. Beighton score ≥ 5 from puberty up to 50 years of age
3. Beighton score ≥ 4 in persons older than 50 years

Add one point if five-point questionnaire is positive (i.e., two or more yes answers)

Five-point questionnaire:

Five-point questionnaire is positive if patient answers yes to two or more questions

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

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 2.12,21 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.17 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 2.12,21 Patients with systemic manifestations (Table 322,25,26-38) 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.30

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.3,40,41 Diagnostic criteria for hypermobile EDS are listed in Figure 2.46 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**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>History</strong></td>
<td></td>
</tr>
<tr>
<td>Clumsiness, motor or speech delay in childhood</td>
<td>Particularly with family history of Ehlers-Danlos syndrome</td>
</tr>
<tr>
<td>Extreme flexibility or double-jointed</td>
<td>Older adults may recall being double-jointed or extremely flexible in childhood</td>
</tr>
<tr>
<td>Recurrent or chronic joint pains</td>
<td>May be limited or widespread</td>
</tr>
<tr>
<td>Joint subluxation or dislocations without significant trauma</td>
<td>Shoulder, knee, and hip most commonly affected</td>
</tr>
<tr>
<td>Recurrent hernias, pelvic organ prolapse, or rectal prolapse</td>
<td>Especially when no other known predisposing condition present</td>
</tr>
<tr>
<td><strong>Physical finding</strong></td>
<td></td>
</tr>
<tr>
<td>Marfanoid habitus</td>
<td>May be present in up to one-third of patients21</td>
</tr>
<tr>
<td>Skin findings</td>
<td></td>
</tr>
<tr>
<td>Unusually soft, silky, or velvety skin</td>
<td></td>
</tr>
<tr>
<td>Mildly hyperextensible skin</td>
<td></td>
</tr>
<tr>
<td>Mild scar atrophy (Figure 1)</td>
<td></td>
</tr>
<tr>
<td>Striae distensae or rubrae</td>
<td></td>
</tr>
<tr>
<td>Plezogenic papules: small subcutaneous fat herniations at lateral heels1</td>
<td>Skin hyperextensibility &gt; 1.5 cm on midvolar forearm of non-dominant arm1</td>
</tr>
<tr>
<td>Scar may be wider or more shallow than normal1</td>
<td></td>
</tr>
<tr>
<td>Striae often appear in adolescence unassociated with weight gain or pregnancy1</td>
<td></td>
</tr>
</tbody>
</table>

*—Features may occur sequentially.

Information from references 1, 2, and 21.
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.\(^1\)

If generalized joint hypermobility is confirmed in patients with suspected hypermobile EDS, the remainder of the hypermobile EDS criteria are sought\(^1\) (Figure 2\(^b\)). 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.

### TABLE 3

**Symptoms Associated with Hypermobile Ehlers-Danlos Syndrome**

<table>
<thead>
<tr>
<th>Organ system</th>
<th>Symptoms/physical findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autonomic(^27,28)</td>
<td>Neurally mediated hypotension/syncope Orthostatic intolerance Postural orthostatic tachycardia syndrome</td>
</tr>
<tr>
<td>Cardiovascular(^29)</td>
<td>Low progressive aortic root dilation Mitral valve prolapse/insufficiency</td>
</tr>
<tr>
<td>Gastrointestinal(^32)</td>
<td>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 Viscerointestines (prolapse of the abdominal viscosa)</td>
</tr>
<tr>
<td>Gynecologic(^26,30)</td>
<td>Disabling dysmenorrhea Dyspareunia Menorrhagia/metrorrhagia Pelvic organ prolapse Urinary stress incontinence</td>
</tr>
<tr>
<td>Mucocutaneous(^31)</td>
<td>Atrophic scars Easy bruising Gingival inflammation/recessions Hernias (inguinal/umbilical/incisional) Hypoplastic lingual frenulum Keratitis pilaris Light blue sclerae Mildly hyperextensible skin Resistance to local anesthetic drugs Velvety/silky/soft skin texture</td>
</tr>
<tr>
<td>Musculoskeletal(^2,32-34)</td>
<td>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 &gt; 1.05) Mild scoliosis, dorsal hyperkyphosis, lumbar hyperlordosis Myofascial pain Nonpostmenopausal reduced bone mass Nonsurgical pectus excavation Recurrent dislocations (e.g., hips, shoulders, temporomandibular, fingers) Recurrent myalgias and cramps Recurrent soft tissue lesions Temporomandibular joint dysfunction</td>
</tr>
<tr>
<td>Neurologic(^32,34,35)</td>
<td>Clumsiness Headache and migraines Impaired memory and concentration Sleep disturbances Somatosensory/central sensitization</td>
</tr>
<tr>
<td>Ocular(^36)</td>
<td>Myopia and/or strabismus Palpebral ptosis</td>
</tr>
<tr>
<td>Psychological(^21,37,38)</td>
<td>Attention-deficit/hyperactivity disorder Chronic fatigue/chronic fatigue syndrome Depression Generalized anxiety Obsessive-compulsive disorder Panic attacks Phobias, kinesiophobia</td>
</tr>
</tbody>
</table>

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

DIAGNOSTIC TESTING

No confirmatory test exists, so hypermobile EDS and hypermobility spectrum disorders remain clinical diagnoses. 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. 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). 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. 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

<table>
<thead>
<tr>
<th>Condition</th>
<th>Distinguishing features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acquired conditions including diffuse degenerative disorders of muscles, joints, or nerves; hypothyroidism; or malnutrition</td>
<td>Suggestive medical history</td>
</tr>
<tr>
<td>Chromosomal and genomic disorders including Down syndrome, aneuploidies (47, XXY; 47, XXX), and several microdeletion and microduplication syndromes</td>
<td>Dysmorphic features, Hypogonadism</td>
</tr>
<tr>
<td>Hereditary cutis laxa: multiple subtypes</td>
<td>Loose, inelastic skin</td>
</tr>
<tr>
<td>Hereditary myopathies: Bethlem, Ullrich, and others</td>
<td>Hypotonia and weakness, Joint hyperlaxity and contractures</td>
</tr>
<tr>
<td>Loeys-Dietz syndrome</td>
<td>Arterial tortuosity and aortic aneurysms, Cleft palate/bifid uvula, Hypertelorism, Hypotonia</td>
</tr>
<tr>
<td>Marfan syndrome, Beals syndrome, MASS phenotype, and arterial tortuosity syndrome</td>
<td>Ectopia lentis in Marfan syndrome, Mitral valve prolapse in MASS phenotype, Progressive ascending aortic dilation, Tortuous medium and large arteries in arterial tortuosity syndrome</td>
</tr>
<tr>
<td>Multiple congenital anomaly or intellectual disability disorders including RASopathies, Kabuki make-up syndrome, and FG syndrome</td>
<td>Multiple congenital anomalies or intellectual disabilities</td>
</tr>
<tr>
<td>Fragile X syndrome</td>
<td>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</td>
</tr>
<tr>
<td>Skeletal dysplasias: osteogenesis imperfecta type I, Larsen syndrome, Desbuquois syndrome, and others</td>
<td>Blue sclerae, Bone fragility, Neonatal joint dislocations</td>
</tr>
</tbody>
</table>

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.\textsuperscript{47,48,50} 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.\textsuperscript{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,\textsuperscript{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

<table>
<thead>
<tr>
<th>Maneuver</th>
<th>Image</th>
<th>Right side scoring</th>
<th>Left side scoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ability to passively dorsiflex the fifth metacarpophalangeal joint $\geq$ 90 degrees</td>
<td><a href="image1.png">Image</a></td>
<td>__ / 1 point</td>
<td>__ / 1 point</td>
</tr>
<tr>
<td>Ability to oppose the thumb to the volar aspect of the ipsilateral forearm</td>
<td><a href="image2.png">Image</a></td>
<td>__ / 1 point</td>
<td>__ / 1 point</td>
</tr>
<tr>
<td>Ability to hyperextend the elbow joint $&gt; 10$ degrees</td>
<td><a href="image3.png">Image</a></td>
<td>__ / 1 point</td>
<td>__ / 1 point</td>
</tr>
<tr>
<td>Ability to hyperextend the knee joint $&gt; 10$ degrees</td>
<td><a href="image4.png">Image</a></td>
<td>__ / 1 point</td>
<td>__ / 1 point</td>
</tr>
<tr>
<td>Ability to place hands flat on the floor by bending forward with knees fully extended</td>
<td><a href="image5.png">Image</a></td>
<td>__ / 1 point</td>
<td></td>
</tr>
</tbody>
</table>

**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.
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.57 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.19 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 epidemiology, risk factors, (pathogenesis or pathogenetic or pathogenic or pathogenic$) 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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References

492 American Family Physician

JOINT HYPERMOBILITY DISORDERS


# Resources on Hypermobility Syndromes

**The Ehlers-Danlos Society**

- Diagnostic criteria for hypermobile Ehlers-Danlos syndrome (fillable PDF)
  

- Patient education videos
  
  https://www.youtube.com/channel/UC652wu-mwi2ghwQN-is7LIQ/videos

- Professional resources
  
  https://www.ehlers-danlos.com/medical-professionals/

- Video demonstrating Beighton Scoring System
  
  https://www.ehlers-danlos.com/assessing-joint-hypermobility/

**Hypermobility Syndromes Association**

- Hypermobility Disorders: An Update for Clinicians
  
  https://www.hypemobility.org/hypermobility-disorders-an-update-for-clinicians

**Royal College of General Practitioners**

- The Ehlers-Danlos Syndromes Toolkit (practical information)
  