Summary

1. Commonest group of disorders in the family of genetically determined heritable disorders of connective tissues. There are 6 types, of which the hypermobility type (III) is the most common.
2. Many affected people do not develop symptoms, or they develop only minor symptoms during their lifetime. Most hypermobile people are not aware of the fact and assume that everyone is as flexible as they are.
3. Apart from joint hypermobility, skin manifestations provide an important clue and include soft, silky skin texture, semi-transparent dermis, and hyperelasticity. Furthermore, patients commonly demonstrate easy bruising, scarring, and poor wound healing.
4. In addition to musculoskeletal and skin manifestations, cardiovascular and GI features, autonomic dysfunction, and features of chronic pain syndrome and marfanoid habitus are often present.
5. Diagnosis is clinical. There is no genetic test that can confirm or refute the diagnosis of the hypermobility type. However, collagen gene testing for the classic and vascular types is available.
6. Recommendations are based on expert opinion. Therapy is tailored to individual need. Multidisciplinary input may be necessary.
7. Many patients live healthy, unaffected lives. The vascular type is associated with a shortened lifespan due to susceptibility to arterial or visceral rupture.

Definition

Ehlers-Danlos syndrome (EDS) is the commonest group of disorders in the family of genetically determined heritable disorders of connective tissues. Caused by mutations affecting genes encoding for or modifying collagen, fibrillin, and/or other matrix proteins (e.g., tenascin), these disorders have similar phenotypes with varying degrees of expression that may include joint hypermobility, skin hyperelasticity, easy bruising, atrophic scars, and marfanoid habitus. There are numerous types of EDS, of which EDS III, or hypermobility type, is the most common. Many clinicians consider it synonymous with benign joint hypermobility syndrome, sharing debilitating, yet often overlooked, associations with autonomic dysfunction, chronic pain, anxiety/phobic states, GI dysmotility, and chronic fatigue (much in the same way as with cases of fibromyalgia). [1] EDS IV, or vascular type, is associated with blood vessel rupture and visceral perforation, and may have severe life-threatening consequences.

Epidemiology

The prevalence of EDS is often reported as 1/10,000 but is likely underestimated. The exact prevalence of the various types of EDS is, however, not known.

EDS III (hypermobility type) is by far the commonest, although joint hypermobility in general is a common finding in the normal population, with prevalence between 10% and 30% (highest among adolescents and young adults, females, and Asian and African racial
groups). [8] A Chilean study of patients with hereditary disorders of connective tissue documented that 92% of patients had joint hypermobility syndrome (EDS III), while 7% had EDS IV (vascular type). [9] A study of the New Zealand white population suggested prevalence of EDS hypermobility type may lie between 0.5% and 1%. [10] A study of female patients attending physiotherapy services in Oman for musculoskeletal complaints recorded hypermobility in 51% of the participant group compared with 30% of the control group. [11] In addition, joint hypermobility syndrome (JHS) was present in 55% of the participant group compared with 21% of the control group, confirming a high prevalence of JHS among subjects with musculoskeletal signs and symptoms attending therapy.

The classic type (EDS I/II) is the second most common, with vascular type (EDS IV) and kyphoscoliotic type (EDS VI) being rare. EDS arthrochalasis type (EDS VII A and B) and dermatosparaxis type (EDS VIIC) are considered extremely rare.

**Aetiology**

It is widely accepted that EDS (in keeping with other heritable disorders of connective tissues) is caused by one or more genetic aberrations affecting genes encoding for, or modifying, connective tissue proteins, such as collagen and matrix proteins (e.g., tenascin). Specific genetic aberrations lead to specific risks, such as severe skin pathology in the classic type (EDS I/II) and vascular collapse due to arteriovenous rupture in the vascular type (EDS IV). [12] In some cases, the gene product modifies a connective tissue protein (e.g., kyphoscoliosis [EDS VI] and dermatosparaxis types [EDS VIIC]). The exact genetic mutation is not always known and the inheritance pattern is variable. In cases of the hypermobility type, the pattern of inheritance is autosomal dominant, so that 50% of offspring of an affected person would be expected to inherit the gene and develop the phenotype. Studies show that the heritability factor (the proportion of phenotypic variation in a population that is attributable to genetic variation among people) of joint hypermobility is >70%. [13] However, inheriting the phenotype does not indicate the occurrence of symptoms. It should be noted that, although most types of EDS are autosomal dominant, the extremely rare types are autosomal recessive (kyphoscoliotic, arthrochalasis [EDS VII A and B], and dermatosparaxis type).

**Pathophysiology**

EDS (in keeping with other heritable disorders of connective tissues) is caused by one or more genetic aberrations affecting genes encoding for, or modifying, connective tissue proteins, such as collagen and matrix proteins (e.g., tenascin). The genetic defect gives rise to a biochemical abnormality, which in turn results in a biomechanical disorder. This has two effects.

1. First, it is responsible for ligament laxity and the resulting hypermobility and enhanced flexibility that is a positive selection factor in performing arts such as dance, gymnastics, and music performance.

2. Second, there is an inherent fragility of connective tissues resulting in a predisposition to injury and a vulnerability to the effects of injury.
Accompanying this is impaired healing, which is often delayed and may be incomplete. Chronic pain and fatigue may ensue, alongside cardiovascular and physical deconditioning.

**Classification**


Clinical classification of Ehlers-Danlos syndromes
Although haploinsufficiency of tenascin XB has been reported in some cases of EDS III (hypermobility type), in almost all patients (92%), no gene mutation has been identified. [5] [6] [7]

**Secondary prevention**

Early patient education, including risk awareness, and advice on physical conditioning may help prevent future injury and development of chronic pain syndrome. Avoiding contact sports and certain physically demanding occupations (e.g., nursing, professional dancing, heavy manual labour) will also help prevent injury and the onset of chronic pain.

All patients (and/or parents) should be provided with detailed information regarding the disorder. Inheritance patterns should be explained and at-risk family members identified. The outcome and natural history of the particular EDS type should be discussed. Advising patients with EDS III (hypermobility type) to avoid having children is not desirable; encouraging them to be alert to childhood and adolescent symptoms is. Patients and their families should also be provided with information on available support groups and other such resources. [Ehlers-Danlos Support Group (UK)] (external link) [Ehlers-Danlos National Foundation] (external link)

**History & examination**

**Key diagnostic factors**

- **presence of risk factors** (common)
  1. Key risk factors include FHx of joint hypermobility or EDS, and genetic mutations.
  2. Pattern of inheritance is usually autosomal dominant, although the extremely rare types are autosomal recessive (kyphoscoliotic, arthrochalasis [EDS VII A and B], and dermatosparaxis type [EDS VII C]).

- **joint hypermobility** (common)
  1. A feature of all types of EDS but is usually less obvious in the vascular type (EDS IV), except in the hands.
  2. Presence of joint hypermobility can be established directly by the Beighton 9-point score [View image] [View image] [View image] [View image] [View image] or indirectly using the 5-question questionnaire. [15] [16]
  3. Hypermobility should be sought in joints outside the 5 sites that form part of the Beighton scoring system, as each hypermobile joint identified adds evidence of joint hypermobility.

- **joint or spine pain** (common)
  1. Patients usually present with multiple-site joint or spinal pain, often brought on by unaccustomed, though not necessarily excessive, physical activity and in the absence of signs of inflammation. Unlike inflammatory joint disease (IJD), there is
no visible joint swelling, warmth, or redness, and no complaint of early morning stiffness unless there is an associated tendonitis. Contrary to what is seen in IJD, the joints move well and, despite pain, may retain their hypermobility.

**motor delay in infancy (common)**
1. Hx of delayed walking (age >18 months), often with omission of crawling and/or substitution of bottom-shuffling, is common in hypermobile infants. Once walking is initiated, the motor delay resolves.

**chronic pain syndrome (common)**
1. Characterised by progressively severe chronic pain, often with fibromyalgia-like tender points on palpation, and accompanied by severe fatigue, autonomic dysfunction, and psychosocial morbidity (anxiety, depression, phobias). A key element is kinesophobia, avoiding movement as a means of avoiding pain.
2. Seen in about one quarter of patients attending hypermobility clinics. [24]
3. Usually occurs due to sudden injury (e.g., whiplash injury resulting from a significant motor vehicle accident) or unusual physical activity during home improvement, sporting activities, or over demanding work activities.

**fatigue (common)**
1. Chronic fatigue is often associated with chronic pain in EDS hypermobile patients.
2. Hypermobile children tire easily and often want to be carried.

**recurrent joint dislocation or subluxation (common)**
1. Because ligaments are lax, joints are unstable and dislocate or sublux easily and repeatedly, in some cases several times a day.

**muscle pain and/or muscle spasm (common)**
1. Tender (or non-tender) muscle spasm can often be palpated in the neck and paravertebral muscles, and sometimes in the muscles surrounding particularly unstable and/or painful joints. [17]
2. Hypermobile children may have joint and/or muscle pain after exercise (growing pains).

**soft, silky skin texture (common)**
1. Skin has a characteristic soft and silky feel. Usually the only skin finding associated with the hypermobility type.

**semi-transparent skin (common)**
1. Skin may have easily visible underlying tendons and veins.

**thin and stretchy double fold of skin (common)**
1. A double fold of skin picked up on the dorsum of the hand is often felt to be thin and, when lifted away from the dorsum of the hand, shows more stretchiness than skin of normal (non-EDS) people. View image

**atrophic scars (common)**
1. Scars (from previous surgery, lacerations, abrasions, chicken pox, or BCG immunisation) have less collagen and are, therefore, usually thin in depth and wide in breadth. Typically they wrinkle when squeezed between the examiner's index finger and thumb.

**easy bruising (common)**
1. Patient often notices bruising but does not recall any precipitating injury.

**stretch marks (common)**
1. Characteristically, stretch marks (striae atrophicae) appear during maximal adolescent growth (between the ages of 11 and 13 years) on thighs, loins, breasts, and, occasionally, shoulders and knees.

**poor wound healing and/or wound dehiscence (common)**
1. Wound healing (involves the laying down of scar tissue or collagen) is delayed and may be incomplete. Wound dehiscence can occur due to fragility of the soft tissues.

**significant injury (common)**
1 Because the tissues are more fragile than normal, they are at particular risk of traumatic or overuse injury. Therefore, injuries that would be inadequate to damage ligament, tendon, muscle, bone, or skin in normal people may result in significant damage.

**hx of delayed onset of local anaesthesia** *(common)*

1 Apparent resistance to the effects of local anaesthetics is seen in about two-thirds of patients. [14]

**Other diagnostic factors**

**muscle hypotonia** *(common)*

1 Muscles may feel doughy on palpation.

**varicose veins** *(common)*

1 Suggests weakness of supporting connective tissue.

**abdominal wall, inguinal, or para-umbilical hernia** *(common)*

1 Suggests weakness of supporting connective tissue.

**uterine or rectal prolapse** *(common)*

1 Suggests weakness of supporting connective tissue.

**orthostatic intolerance** *(common)*

1 Suggests cardiovascular autonomic dysfunction. [19]

2 Delayed hypotension assessed >3 minutes after standing; often associated with acrocyanosis (dusky colour) and swollen legs that resolves on lying flat.

**postural orthostatic tachycardia syndrome (POTS)** *(common)*

1 Greater than 30-bpm increase in pulse on standing or >120 bpm within 10 minutes of head-up tilt-table testing, both in the absence of orthostatic hypotension that might trigger a normal tachycardiac response. [19]

**marfanoid habitus** *(common)*

1 May be present in association with EDS (usually incomplete). Common finding in the hypermobility and the kyphoscoliotic types, but is not necessary for diagnosis.

2 Features include: high arched palate; arachnodactyly; pectus excavatum or carinatum; scoliosis; arm span to height ratio >1.05; tall stature with lower limb length (floor to pubis) to upper body (pubis to crown) ratio >0.89; foot length (heel to first toe) to height ratio >0.15; hand length (wrist crease to third finger) to height ratio >0.11. [18]

**GI manifestations** *(common)*

1 Patients may have signs and symptoms suggesting a GI disorder, such as gastritis/ GORD (heartburn and acid regurgitation), gastroparesis (chronic nausea, vomiting, epigastric pain, bloating, and early satiety), irritable bowel syndrome (recurrent abdominal pain or discomfort associated with a change in stool frequency or form; pain or discomfort may be relieved by defecation), or rectal evacuatory disorder (characterised by difficulty with defecation, with or without need for manual evacuation and laxatives). [20] [21]

**eye abnormalities** *(uncommon)*

1 Suggests weakness of supporting connective tissue.

2 Lids appear drooping, but this does not extend to ptosis.

3 Anti-mongoloid slant is a condition in which the nasal corners of the palpebral fissure are higher than the temporal corners, as opposed to the typical mongoloid slant.

4 Blue sclera is due to thinning of the sclera. It is a non-specific feature of collagen deficiency.

5 Myopia is common in hypermobility syndromes.

**mid-systolic click or late systolic murmur** *(uncommon)*
May suggest mitral valve prolapse due to weak, lax, and less-effective connective tissues.

**Orthostatic hypotension (uncommon)**
1. Suggests cardiovascular autonomic dysfunction.
2. Rapid drop in blood pressure >20/10 mmHg on standing.

**Risk factors**

**FHx of joint hypermobility or EDS**
1. In cases of EDS III (hypermobility type) the pattern of inheritance is autosomal dominant, so that 50% of offspring of an affected person would be expected to inherit the gene and develop the phenotype. Studies show that the heritability factor (the proportion of phenotypic variation in a population that is attributable to genetic variation among people) of joint hypermobility is >70%. However, inheriting the phenotype does not indicate the occurrence of symptoms. Most affected people do not develop symptoms at all, or they develop only minor symptoms during their lifetime.
2. Although most types of EDS are autosomal dominant conditions, the extremely rare types (kyphoscoliotic [EDS VI], arthrochalasis [EDS VII A and B], dermatosparaxis [EDS VIIC]) are autosomal recessive.

**Genetic mutations**
1. EDS (in keeping with other heritable disorders of connective tissues) is caused by one or more genetic aberrations affecting genes encoding for, or modifying, connective tissue proteins, such as collagen and matrix proteins (e.g., tenascin). Specific genetic aberrations lead to specific risks, such as severe skin pathology in EDS I/II (classic type) and vascular collapse due to arteriovenous rupture in EDS IV (vascular type). In some cases the gene product modifies a connective tissue protein (e.g., kyphoscoliosis [EDS VI] and dermatosparaxis types [EDS VIIC]).
2. The exact genetic mutation is not always known.

**Diagnostic tests**

1st tests to order

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
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</table>
**clinical diagnosis**
EDS is present from birth and is often diagnosed in childhood, but in some cases may be detected only in adulthood. Musculoskeletal and skin manifestations are the primary features; cardiovascular and GI autonomic dysfunctions, as well as other manifestations, are considered supportive findings. Apart from joint hypermobility, no feature is universally present in any form of EDS. Many affected people do not develop symptoms at all, or they develop only minor symptoms during their lifetime. The history should also include the nature and effectiveness of pain relief, interventions to date, and any past experiences with local anaesthetic use, as apparent resistance to the effects of local anaesthetics is seen in about two-thirds of patients. [14]

**Tests to consider**

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
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<tbody>
<tr>
<td><strong>genetic testing</strong></td>
<td>There is no genetic test that can confirm or refute the diagnosis of EDS III (hypermobility type). However, collagen gene testing for the classic and vascular types is available. [22]</td>
</tr>
<tr>
<td><strong>tilt-table testing</strong></td>
<td>Cardiovascular autonomic abnormalities may be present; most experience is with EDS III (hypermobility type). Tachycardia in the absence of orthostatic hypotension suggests postural orthostatic tachycardia syndrome.&gt;30-bpm increase in pulse on standing or &gt;120 bpm within 10 minutes of head-up suggests postural orthostatic tachycardia syndrome</td>
</tr>
<tr>
<td><strong>x-ray spine</strong></td>
<td>Usually necessary in patients with spinal pain or with scoliosis noted on physical examination. may show scoliosis, spondylolisthesis</td>
</tr>
</tbody>
</table>
**echocardiogram**
Cardiac valve anomalies are seen more frequently with EDS III (hypermobility type). Echocardiogram is necessary to exclude mitral valve prolapse and to assess aortic root diameter. Ideal frequency of echocardiogram (to monitor aortic root) is unknown; probably more important to repeat in childhood and adolescence than in adulthood.

**GI imaging and endoscopy**
Barium enema and colonoscopy may be necessary to exclude associated large bowel pathology, such as carcinoma, inflammatory bowel disease, polyps. CT colography may be considered as a less invasive alternative to conventional colonoscopy. Evacuating proctography may identify rectocele, intussception, and/or megarectum.

<table>
<thead>
<tr>
<th>Differential diagnosis</th>
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<tbody>
<tr>
<td>Condition</td>
</tr>
<tr>
<td>EDS-related GI dysmotility</td>
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<tr>
<td>Marfan's Syndrome</td>
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</table>

1. Aortic regurgitation and aortic root dilation are common findings on echocardiogram; may also reveal ascending aortic dissection.

2. MRI of the lumbar spine may show dural ectasia.

3. Molecular analysis of peripheral blood sample shows fibrillin I and II abnormalities.

4. Pneumothorax and emphysematous bullae on CXR may be noted.

18. Lens
| Fibromyalgia | 1 | Chronic pain syndrome diagnosed by the presence of widespread body pain (front and back, right and left, both sides of the diaphragm) for at least 3 months in addition to tenderness (digital palpation at a force of about 4 kg) of at least 11 out of 18 designated tender-point sites. [25] | 1 | Diagnosis is clinical. |
Chronic fatigue syndrome

Characterized by persistent fatigue and other associated symptoms (e.g., musculoskeletal pain, sleep disruption, memory impairments) lasting at least 6 months. The fatigue is not related to other medical conditions, disease processes, or identifiable biological causes. Sleep, rest, and activity restriction do not improve symptoms.

Patients may present with a low-grade fever, tender lymph nodes, muscle pain/joint stiffness on palpation, tachycardia, hyperventilation, and/or orthostatic hypotension.
<table>
<thead>
<tr>
<th>Loeys-Dietz syndrome</th>
<th>1</th>
<th>Autosomal dominant genetic syndrome that has many features similar to Marfan's syndrome. [26]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
<td>Pronounced skeletal deformities have been reported in children. Key skeletal elements include club feet, scoliosis, upper cervical deformity, and knee or elbow hyperextensibility. Presence of hypertelorism, cleft palate, or bifid uvula should prompt referral to a geneticist. [26]</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Genetic testing reveals mutations in the genes encoding transforming growth factor beta receptor 1 or 2.</td>
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<tr>
<td></td>
<td>2</td>
<td>Aortic root dilation is a common finding on echocardiogram.</td>
</tr>
<tr>
<td><strong>Thrombotic thrombocytopenic purpura</strong></td>
<td>1</td>
<td>Neurological examination might reveal focal abnormalities, and presence of pallor (anaemia) and petechiae can support the diagnosis.</td>
</tr>
<tr>
<td><strong>Idiopathic thrombocytopenic purpura</strong></td>
<td>1</td>
<td>Isolated thrombocytopenia in the absence of other causes; thought to be due to an autoimmune phenomenon. Typically found in middle-aged women, often with a preceding viral illness, who present with thrombocytopenia with or without bleeding.</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Physical examination is usually normal. Petechiae may be present on mucosal membranes or the lower limbs.</td>
</tr>
<tr>
<td>Condition</td>
<td>Presentation</td>
<td>Diagnosis</td>
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<tr>
<td>von Willebrand's disease</td>
<td>Usually presents with mucocutaneous bleeding.</td>
<td>Diagnosis is based on various tests, including von Willebrand factor (VWF) antigen, VWF activity (ristocetin co-factor or collagen-binding assay), factor VIII assay, and VWF multimers.</td>
</tr>
<tr>
<td>Corticosteroid excess</td>
<td>One of the most common causes of poor wound healing; hx of chronic corticosteroid use usually present.</td>
<td>Diagnosis is clinical.</td>
</tr>
<tr>
<td><strong>Porphyria cutanea tarda</strong></td>
<td>1</td>
<td>Results from an acquired, substantial deficiency of uroporphyrinogen decarboxylase in the liver.</td>
</tr>
<tr>
<td>2</td>
<td>Recognised by blistering and crusted skin lesions on the back of hands and other sun-exposed areas of the body. Other common features include skin fragility with minor trauma causing blister formation, hypertrichosis, skin hyperpigmentation, and dark or reddish urine.</td>
<td>1</td>
</tr>
</tbody>
</table>

| **Epidermolysis bullosa** | 1 | Inherited mechanical fragility of the skin and epithelial tissues. Presents as recurrent erosions, blisters, and scars. | 1 | Diagnosis is confirmed by immunofluorescence antigenic mapping performed on a cryopreserved skin biopsy specimen, obtained from a freshly induced lesion. |
**Vitamin C deficiency**

1. Scurvy is a rare disorder, with epidemics typically affecting populations subject to famine or displacement during wartime.

2. Most key clinical manifestations are related to impaired collagen synthesis. These include bleeding complications (spontaneous petechiae and ecchymoses), friable gingiva and loose teeth, bone pain, and joint effusions.

1. Low levels of serum, leukocyte, and whole blood ascorbic acid confirm the diagnosis.

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**Step-by-step diagnostic approach**

The diagnosis is based on clinical grounds. EDS is present from birth and is often diagnosed in childhood, but in some cases may be detected only in adulthood. Musculoskeletal and skin manifestations are the primary features; cardiovascular and GI autonomic dysfunctions, as well as other manifestations, are considered supportive findings. Apart from joint hypermobility, no feature is universally present in any form of EDS. Many affected people do not develop symptoms at all, or they develop only minor symptoms during their lifetime. The history should also include the nature and effectiveness of pain relief, interventions to date, and any past experiences with local anaesthetic use, as apparent resistance to the effects of local anaesthetics is seen in about two-thirds of patients. [14]
There is no genetic test that can confirm or refute the diagnosis of EDS III (hypermobility type). However, collagen gene testing for EDS I/II (classic) and EDS IV (vascular) types is available.

**Classification**

Clinical classification of Ehlers-Danlos syndromes

Family history of joint hypermobility is highly suggestive; the pattern of inheritance is usually autosomal dominant type, so that 50% of offspring of an affected person would be expected to inherit the gene and develop the phenotype. However, the extremely rare types of EDS are autosomal recessive (kyphoscoliotic, arthrochalasis, and dermatosparaxis types).

**Musculoskeletal manifestations**

*Joint hypermobility*

1. This is considered a feature of all types of EDS but is usually less obvious in EDS vascular type (except in the hands). Most hypermobile people are not aware of the fact and assume that everyone is as flexible as they are.

2. A history of delayed walking (beyond 18 months of age), often with the omission of crawling and/or the substitution of bottom-shuffling, is common in hypermobile infants. They are often clumsy and fidgety. Once walking is initiated, the motor delay resolves. Hypermobile children tire easily and often want to be carried; they may have joint and/or muscle pain after exercise (growing pains).

3. The presence of joint hypermobility can be established directly by calculating the Beighton 9-point score, which is based on the ability to perform a series of manoeuvres. A score of 5/9 or higher is usually taken to indicate generalised hypermobility. [15]

1. Dorsiflex the 5th metacarpophalangeal joint to 90° or greater (1 point for each side). View image

2. Oppose the thumb to the volar aspect of the ipsilateral forearm (1 point for each side). View image

3. Hyperextend the elbow to 10° or greater (1 point for each side). View image

4. Hyperextend the knee to 10° or greater (1 point for each side). View image

5. Place the hands flat on the floor with the knees fully extended (1 point). View image

4. Hypermobility should also be sought in joints outside the 5 sites that form part of the Beighton scoring system, as each hypermobile joint identified will add evidence of joint hypermobility. Some useful manoeuvres in this context include:

1. Passive external rotation of the shoulder to 90° or greater
2 Lateral flexion of cervical spine to 60° or greater
3 Rotation of thoracic spine to 90° or greater
4 Dorsiflexion of first metatarsophalangeal joint to 90° or greater
5 Flattening on the longitudinal arch of the feet with pronation of the foot on weight-bearing.

Joint hypermobility can also be determined indirectly by using the 5-question questionnaire. An answer in the affirmative to 2 or more questions suggests hypermobility with a sensitivity of 80% to 85% and a specificity of 80% to 90%. [16]

1 Can you now (or could you ever) place your hands flat on the floor without bending your knees? View image
2 Can you now (or could you ever) bend your thumb to touch your forearm? View image
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?

It is important to be aware that this list of manoeuvres is by no means complete, and any or all joint laxity elicited on physical examination may be relevant. Furthermore, it should be noted that various factors such as male gender, older age, muscle spasm, prior injury/surgery, and arthritic degeneration can all mask underlying joint laxity.

Joint pains

1 Older patients usually present with multiple-site joint or spinal pain often brought on by unaccustomed, though not necessarily excessive, physical activity and in the absence of signs of inflammation.

2 Unlike inflammatory joint disease (IJD) there is no visible joint swelling, warmth, or redness and no complaint of early morning stiffness unless there is an associated tendonitis. Contrary to what is seen in IJD, the joints move well and, despite pain, may retain their hypermobility.

Joint dislocation or subluxation

1 Because ligaments are lax, joints are unstable and dislocate or sublux easily and repeatedly, in some cases several times a day. Therefore, recurrent joint dislocation or subluxation is also a common presentation.
Muscle spasm

1 Tender (or non-tender) muscle spasm can often be palpated in the neck and paravertebral muscles, and sometimes also in the muscles surrounding particularly unstable and/or painful joints. [17]

Chronic pain syndrome

1 This may develop as a consequence of trauma and is characterised by progressively severe chronic pain (whole-body pain not relieved by analgesics is common), often with fibromyalgia-like tender points on palpation, accompanied by severe fatigue, autonomic dysfunction, and psychosocial morbidity (anxiety, depression, phobias). A key element is kinesophobia, avoiding movement as a means of avoiding pain. The result is a progressive decline in health and quality of life.

Marfanoid habitus

1 This may be present in association with EDS (usually incomplete). It is a common finding in hypermobility and kyphoscoliotic types but is not necessary for diagnosis of EDS. Features include: [18]

1 High arched palate

2 Arachnodactyly

1 Wrist sign (Walker): positive if able to wrap the thumb and fifth finger of one hand around the opposite wrist such that the nail beds of the digits overlap with each other.

2 Thumb sign (Steinberg): positive if the adducted thumb across the palm projects beyond the ulnar border in the clenched hand.

3 Pectus excavatum or carinatum

4 Scoliosis: a sign of EDS VI (kyphoscoliotic type); in other EDS variants and in joint hypermobility syndrome it may be present, albeit to a milder degree.

5 Arm span to height ratio >1.05

6 Tall stature with lower limb length (floor to pubis) to upper body (pubis to crown) ratio >0.89

7 Foot length (heel to first toe) to height ratio >0.15

8 Hand length (wrist crease to third finger) to height ratio >0.11

Weakness of supporting structures

1 This is due to weak, lax, and less-effective connective tissues, and can manifest as:
1. Eye signs: drooping eyelids or anti-mongoloid slant, blue sclera, myopia
2. Muscle hypotonia: muscles may feel doughy on palpation
3. Mitral valve prolapse: presence of mid-systolic click or late systolic murmur on cardiac auscultation
4. Varicose veins
5. Abdominal wall, inguinal, or para-umbilical hernia
6. Uterine or rectal prolapse.

2. Significant injury: because the tissues are more fragile than normal, they are at particular risk of traumatic or overuse injury. Therefore, injuries that would be inadequate to damage ligament, tendon, muscle, bone, or skin in normal people may result in significant damage.

**Skin manifestations**

Examination of the skin is the most reliable method of diagnosing EDS. The skin texture usually feels soft and silky to the touch (usually the only skin finding associated with the hypermobility type). The dermis is often semi-transparent. Easy bruising is common; the patient often notices bruising but does not recall any precipitating injury. A double fold of skin picked up on the dorsum of the hand is frequently felt to be thin. In addition, when the double fold of skin is lifted away from the dorsum of the hand, it shows more stretchiness than the skin of normal (non-EDS) people. View image

Characteristically, stretch marks (striae atrophicae) appear during the age of maximal adolescent growth (between the ages of 11 and 13 years) on thighs, loins, breasts, and occasionally shoulders and knees.

Scars (from previous surgery, lacerations, abrasions, chicken pox, or BCG immunisation) are typically atrophic; they have less collagen, are usually thin in depth and wide in breadth, and wrinkle when squeezed between the examiner's index finger and thumb.

Patients may also present with delayed or incomplete wound healing, usually involving the laying down of scar tissue or collagen. In addition, wound dehiscence can occur due to fragility of the soft tissues.

**Autonomic abnormalities**

Cardiovascular

1. Most experience is with the hypermobility type. Abnormalities include:

   1. Orthostatic hypotension: rapid drop in blood pressure of >20/10 mmHg on standing
2 Orthostatic intolerance: delayed hypotension assessed >3 minutes after standing; often associated with acrocyanosis (dusky colour) and swollen legs (due to pooling of blood) that resolves on lying flat.

3 Postural orthostatic tachycardia syndrome: >30-bpm increase in pulse on standing or >120 bpm within 10 minutes of head-up tilt-table testing, both in the absence of orthostatic hypotension that might trigger a normal tachycardiac response. [19]

Gastrointestinal

1 Patients may have signs and symptoms suggesting a GI disorder such as gastritis/GORD (heartburn and acid regurgitation), gastroparesis (chronic nausea, vomiting, epigastric pain, bloating, and early satiety), irritable bowel syndrome (recurrent abdominal pain or discomfort associated with a change in stool frequency or form; pain or discomfort may be relieved by defecation), or rectal evacuatory disorder (characterised by difficulty with defecation, with or without need for manual evacuation and laxatives). [20] [21]

Investigations

Diagnosis is usually based on clinical grounds; therefore, investigations are primarily supportive. However, collagen gene testing for the classic and vascular types is available and may confirm diagnosis. [22]

Plain film x-ray of the spine is usually necessary in patients presenting with spinal pain or with scoliosis noted on physical examination.

An echocardiogram helps rule out mitral valve prolapse and aortic root dilation, which has been detected on echocardiogram in patients with both classic and hypermobility types, and should be performed periodically, particularly in childhood and adolescence. [23]

Tests for GI autonomic dysfunction and associated GI conditions may be considered; they include barium enema, colonoscopy, CT colography, and/or evacuating proctography.

Diagnostic criteria

Positive Beighton and/or Brighton scores are helpful but not required to establish a diagnosis.

Beighton 9-point scoring system for joint hypermobility [15]

Based on ability to perform a series of manoeuvres:

1 Dorsiflex the 5th metacarpophalangeal joint to 90° or greater (1 point for each side) View image

2 Oppose the thumb to the volar aspect of the ipsilateral forearm (1 point for each side) View image

3 Hyperextend the elbow to 10° or greater (1 point for each side) View image
4 Hyperextend the knee to 10° or greater (1 point for each side) View image

5 Place the hands flat on the floor with the knees fully extended (1 point). View image

A score of 5/9 or higher is usually taken to indicate generalised hypermobility.

1998 Brighton criteria for benign joint hypermobility syndrome [27]

Relevant because many clinicians consider EDS hypermobility type to be synonymous with benign joint hypermobility syndrome (BJHS).

**Major criteria**

1 Beighton score 4/9 or higher (either currently or historically)

2 Arthralgia for >3 months in 4 or more joints.

**Minor criteria**

1 Beighton score of 1, 2, or 3/9 (0, 1, 2, or 3 if aged 50 years or older)

2 Arthralgia in 1 to 3 joints, or back pain or spondylosis, spondylolysis/spondylolisthesis

3 Dislocation in >1 joint, or in 1 joint on >1 occasion

4 Three or more soft-tissue lesions (e.g., epicondylitis, tenosynovitis, bursitis)

5 Marfanoid habitus (tall, slim, span >height; upper segment to lower segment ratio <0.89, arachnodactyly)

6 Skin striae, hyperextensibility, thin skin, or abnormal scarring

7 Eye signs: drooping eyelids, myopia, or anti-mongoloid slant

8 Varicose veins, hernia, or uterine/rectal prolapse.

BJHS is diagnosed in the presence of 2 major criteria, or 1 major and 2 minor criteria, or 4 minor criteria. Two minor criteria suffice where there is an unequivocally affected first-degree relative.


Clinical classification of Ehlers-Danlos syndromes
Although haploinsufficiency of tenascin XB has been reported in some cases of EDS III (hypermobility type), in almost all patients (92%), no gene mutation has been identified. [5] [6] [7]
Case history #1
A 24-year-old woman presents with "whole-body" pain for the past year that is not controlled by analgesics. She also has palpitations and dizziness when she gets out of bed in the morning and feels very tired, to the extent that she has to rest after work. She works as a teacher and was formerly an enthusiastic athlete and dancer. In infancy, her legs would tire easily and she would insist on being carried. On several occasions she twisted her ankles badly, limping for several weeks. By 16 years of age, her ankles were so "weak" she was forced to give up dancing and athletics. She has a history of recurrent dislocation of the left shoulder. The initial episode occurred when she missed her step and fell down a flight of stairs, but now the shoulder dislocates on minimal provocation, and quite often she has to go to the emergency department to have it reduced.

Case history #2
An 8-year-old girl is brought by her mother to see her primary care physician because the girl has pain in her legs at night, especially after physical activities. Her mother reports that as an infant the girl never crawled but "bottom-shuffled" instead. She did not walk until 20 months of age and then tended to fall over easily. Her mother noticed that the girl was more "bendy" than her older siblings and also clumsier, always bumping into furniture. Constantly fidgeting, she was always changing position. She hated walking around shopping centres, preferring to be carried or pushed in the buggy. Her ankles are unstable, and she is often going over on them. She walks with very flat feet and has difficulty keeping up with her friends. She holds a pen in an awkward manner, and her hand gets very tired after writing half a page.

Treatment Options

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Treatment line</th>
<th>Treatment details</th>
</tr>
</thead>
<tbody>
<tr>
<td>all patients</td>
<td>1st</td>
<td><strong>general recommendations</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1. No good studies are available to establish the value (or lack thereof) of any particular treatment. All recommendations are based on expert opinion.</td>
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<tr>
<td></td>
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<td>2. Asymptomatic patients do not require any specific treatment. However, all patients should be advised to avoid contact sports because of the risk of injury to soft tissue and bone. In addition, fitness should be encouraged to minimise risk of injury. Certain occupations are physically demanding and are best avoided such as nursing, professional dancing, and heavy manual labour.</td>
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</table>
All patients (and/or parents) should be provided with detailed information regarding the disorder. Inheritance patterns should be explained and at-risk family members identified. The outcome and natural history of the particular EDS type should be discussed. Advising patients with EDS III (hypermobility type) to avoid having children is not desirable; encouraging them to be alert to childhood and adolescent symptoms is. Patients and their families should also be provided with information on available support groups and other such resources. [Ehlers-Danlos Support Group (UK)](external link) [Ehlers-Danlos National Foundation](external link)

A standard approach to pain management applies. There have been no randomised controlled trials in EDS, and clinicians tend to follow guidance from the management of fibromyalgia.

1. NSAIDs, skeletal muscle relaxants, and opioid analgesics play a role in treating joint, muscle, and/or spine pain.

2. Other options include drugs used for neuropathic pain, serotonin-noradrenaline (serotonin-norepinephrine) reuptake inhibitors, and tricyclic antidepressants.

3. Corticosteroid injections and/or local anaesthetic agents may be considered when oral analgesics do not adequately relieve pain (e.g., trigger-point injections, bursa injections, intra-articular injections). [14] Local anaesthetic agents, in a higher than average dose, provide relief despite apparent resistance.

4. Nerve-root blocks and spinal-cord stimulators may be useful adjuncts in select cases of intractable chronic pain.
The principles of therapy include: 1) restoring normal range of motion for that particular patient, even if it is hypermobile, 2) restoring efficient and effective movement patterns throughout the full range of motion, including the hypermobile range (this involves correcting and preventing movement dysfunction and regaining joint stability), 3) educating, reassuring, advising, and problem-solving, 4) improving general fitness to avoid de-conditioning (usually achieved with muscle toning to help stabilise loose joints, and avoiding high-resistance strengthening-type exercises).

Each patient requires a detailed assessment and individualised programme. Techniques may include neural biofeedback, and therapies often involve the principles of Pilates, the Alexander technique, and tai chi. Myofascial release (a form of soft-tissue therapy) may be performed to reduce muscle spasm.

Chronic and unremitting pain with profound physical de-conditioning may require a multidisciplinary pain management programme involving CBT. Furthermore, with chronic pain may come reactive depression, anxiety, and/or phobic states requiring short-term antidepressant and/or anxiolytic therapy to support or facilitate other therapeutic interventions.

While physiotherapy and occupational therapy encourage strengthening and endurance with a goal of avoiding supports and splints (the best splint is the patient's own musculature), supports may inevitably be required to stabilise non-responding joints or to support one region in order that joints above and below may be strengthened without undue stress (e.g., strapping the knee to focus on re-aligning and stabilising the hip and ankle). In addition, orthotics are valuable in re-aligning the foot and reducing pain.

Often involves closed reduction as soon as possible to decrease potential complications, including soft-tissue injury, articular surface injury, and neurovascular compromise. Reduction usually requires sedation and analgesia. A period of immobilisation should be followed by active motion exercises and isometric strengthening exercises.
For patients with autonomic dysfunction and weakness of supporting structures (e.g., uterine or rectal prolapse; myopia; abdominal wall, inguinal, or para-umbilical hernia; mitral valve prolapse) referral to specialist cardiac, autonomic neurology, gastroenterology, ophthalmological, and/or surgical services should be made if there are specific concerns.
GI disorders are treated as for non-EDS patients. For example, antacids for gastritis or promotility agents for gastroparesis; fibre, avoiding certain food products, and smooth muscle relaxants for irritable bowel syndrome. These conditions can usually be managed by a primary care physician.

1 For abnormal gut flora, amoxicillin/clavulanate or ciprofloxacin plus metronidazole can be given for 10 days.

2 For constipation, docusate sodium or glycerin suppositories are an option.

3 For slow transit, prokinetic agents (such as domperidone or metoclopramide) enhance GI motility, especially for those patients with reflux/dysphagia.

4 A probiotic (such as VSL3) may also be considered for slow-transit issues.

5 Low-FODMAP diet may be considered for those suffering from bloating. This refers to a diet low in fermentable oligo-, di-, and mono-saccharides, and polyols. These are short-chain carbohydrates that are osmotically active, causing diarrhoea after ingestion by dragging water from the intestinal vessels into the intestinal lumen. Fermentation by intestinal bacteria then yields large volumes of gases (hydrogen or carbon dioxide) leading to bloating.

**Primary Options**

- **abnormal gut flora**
  - amoxicillin/clavulanate: 875 mg orally twice daily for 10 days
  - or
ciprofloxacin: 500 mg orally twice daily for 10 days
  -- AND --
  - metronidazole: 250 mg orally three times daily for 10 days

- **constipation**
  - docusate sodium: 100 mg orally once or twice daily
  - or
glycerol rectal: 1 suppository inserted into rectum once or twice daily when required

- **slow transit**
  - domperidone: 10-20 mg orally three times daily
  - or
  - metoclopramide: 10 mg orally four times daily

**Monitoring**
Each patient is judged individually. Pain management should be reviewed regularly to determine the efficacy and tolerability of medication. Those who do not respond adequately may require CBT. Follow-up after any physical rehabilitation programme and/or CBT should be at 6 and 12 months after therapy. Assessment sooner than this is unlikely to have allowed sufficient time for positive effect.

Review at 6 to 12 weeks after an acute injury is advised to ensure that the injury is settling and unlikely to become a chronic problem.

Introducing therapies for the management of autonomic dysfunction should also be assessed regularly until the clinician is confident that the therapy is well tolerated and efficacious. Thereafter, a 6-month review is recommended. Periodic echocardiogram to assess for mitral valve prolapse and measuring the aortic root is advised, especially for children and adolescents, but the frequency of this investigation has not been determined.

### Patient Instructions

Patients should be advised to avoid contact sports because of the risk of injury to soft tissue and bone. In addition, fitness should be encouraged, as this can minimise risk of injury. Certain occupations are physically demanding and are best avoided, such as nursing, professional dancing, and heavy manual labour.

Patient information is also available. [Ehlers-Danlos Support Group (UK)](external link)

### Complications

<table>
<thead>
<tr>
<th>Complication</th>
<th>Timeframe</th>
<th>Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>reduced quality of life</td>
<td>long term</td>
<td>medium</td>
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<tr>
<td>The musculoskeletal manifestations of EDS III (hypermobility type) have been found to have a marked effect on patient physical activity and quality of life.</td>
<td>long term</td>
<td>low</td>
</tr>
<tr>
<td>degenerative arthritis</td>
<td>long term</td>
<td>low</td>
</tr>
<tr>
<td>Can occur, especially if steps are not taken to reduce joint instability.</td>
<td>long term</td>
<td>low</td>
</tr>
<tr>
<td>surgery-related complications</td>
<td>variable</td>
<td>high</td>
</tr>
<tr>
<td>-------------------------------</td>
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<tr>
<td>Wound suturing may be problematic due to tissue friability. Bleeding risk should always be considered before performing a surgical procedure in these patients, particularly in those with EDS IV (vascular type). In addition, surgical procedures may be further complicated by lack of or reduced response to local anaesthetic agents.</td>
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</table>

<table>
<thead>
<tr>
<th>pregnancy complications</th>
<th>variable</th>
<th>medium</th>
</tr>
</thead>
<tbody>
<tr>
<td>see our comprehensive coverage of Overview of pregnancy complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unlike the vascular form (EDS IV), EDS III (hypermobility type) is not associated with heart disease or major hazards (e.g., bowel rupture) during pregnancy and labour. However, the following can occur:</td>
<td></td>
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<tr>
<td>1) joint and spinal pains may increase during the course of the pregnancy, 2) membranes can rupture prematurely, with consequent premature labour and delivery; labour may be rapid, 3) the apparent resistance to the effects of local anaesthetics can cause problems during epidural anaesthesia or infiltration for repair of a tear or episiotomy, 4) healing of tear or episiotomy may be impaired and/or prolonged, and surgical technique may need to be modified accordingly, 5) lactation and care of the newborn baby may be more taxing than for non-EDS mothers, 6) pelvic floor problems (e.g., uterine prolapse) may occur in later life so that the practise of postnatal exercises is particularly important.</td>
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rupture of blood vessels or organs
Large or medium-sized arteries, intestines, uterus, and/or tendons can spontaneously rupture or tear, primarily in the vascular type (EDS IV). Sudden death may be the outcome. Surgery and invasive radiology are therefore best avoided in these patients as far as possible.

Prognosis
Many patients with EDS live healthy, unaffected lives. Only the vascular type (EDS IV) is associated with a shortened lifespan. [4]

Patients with chronic pain syndrome and/or severely disruptive recurrent injury and joint dislocation can be immensely challenging therapeutically. Some patients have been known to excel in recovery to normal daily function with good quality of life, while others remain severely disabled with continued need for adjustments medically and psycho-socially. [17]

Patients with the vascular type (EDS IV) have a mean survival age of 40 years, with patients succumbing to arterial or visceral rupture. Surgery and invasive radiology are best avoided due to the risk of life-threatening complications. [4] Pregnancy in these patients is hazardous but success is well documented.