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# Characteristics, Diagnosis, and Management of Ehlers-Danlos Syndromes
## A Review

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**IMPORTANCE** Ehlers-Danlos syndromes (EDSs) are a group of heritable connective tissue disorders. Patients with EDSs can develop excessive facial rhytids, nasal deformities, and facial scarring, for which they may seek consultation with a facial plastic surgeon. Ehlers-Danlos syndromes can be associated with serious surgical complications and should be identified preoperatively to facilitate optimal treatment. To our knowledge, no management guidelines for patients with EDSs exist in the facial plastic surgery literature. We present a review of the literature and management recommendations for the facial plastic surgeon.

**OBSERVATIONS** We performed a PubMed/MEDLINE search for all publications in the English language related to surgical experience in patients with EDSs. A total of 37 publications (including reviews and case series) were included. Ehlers-Danlos syndromes are more common than appreciated, with an overall point prevalence between 1 in 2500 and 1 in 5000 according to existing literature. There are 6 main subtypes of EDSs that have significant phenotypic heterogeneity. Patients with classic type and hypermobile EDS (the 2 most common subtypes) can typically undergo elective facial plastic surgery without major complications. However, specific preoperative, intraoperative, and postoperative issues, as outlined in this review, must be taken into consideration. Vascular EDS should serve as a contraindication to elective surgery given its potential for life-threatening complications.

**CONCLUSIONS AND RELEVANCE** Because of their skin laxity, patients with EDSs may present more frequently to facial plastic surgeons' offices. Simple screening questions can help the surgeon identify potential patients with EDSs. Treatment should be individualized and performed with extreme care to ensure optimal outcomes.

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The Ehlers-Danlos syndromes (EDSs) are a group of heritable connective tissue disorders that can have a profound impact on facial plastic surgery outcomes. The hallmark of EDSs is defective connective tissue synthesis, which manifests principally as skin hyperelasticity, joint hypermobility, easy bruising, and tissue fragility.[1] Patients with EDSs often have increased skin rhytids and aberrant scarring, and may seek consultation with the facial plastic surgeon. However, EDSs are associated with a variety of potential surgical complications, including wound dehiscence, excessive bleeding, and sometimes life-threatening complications, such as vascular or tracheal rupture.[2-7] Therefore, it is critical to identify patients with EDSs and provide them with proper treatment to avoid possibly catastrophic consequences.

The reported prevalence of EDSs ranges from approximately 1 in 150 000 in the southern English population,[8] to up to 9% in some US populations.[9] However, EDSs are likely underdiagnosed owing to their phenotypical heterogeneity, and milder variants can go undetected. The aggregate frequency of EDS has been estimated at up to 1 in 2500 to 1 in 5000 births.[1,10]

While some case reports exist on the treatment of EDS patients in general and orthopedic surgery, few reports and no treatment guidelines exist for these patients in the facial plastic surgery literature. This review aims to provide a practical guide on the diagnosis and management of patients with EDS for the facial plastic surgeon.

## Methods

We performed a detailed literature search using PubMed and MEDLINE of all publications in the English language up to November 2016. The search terms used include *Ehlers-Danlos syndrome AND plastic surgery*, *Ehlers-Danlos syndrome AND surgery*, *Ehlers-Danlos syndrome AND rhinoplasty*, *Ehlers-Danlos syndrome AND rhytidectomy*, *Ehlers-Danlos syndrome AND face-lift*, *Ehlers-Danlos syndrome AND blepharoplasty*, *Ehlers-Danlos syndrome AND graft*, *Ehlers-Danlos syndrome AND flap*, *Ehlers-Danlos syndrome AND free tissue*, and *Ehlers-Danlos syndrome AND laser*. The abstracts gen-

Table 1. Major Subtypes of Ehlers-Danlos Syndromes[a]

| Major Subtype | Major Diagnostic Criteria (and Other Clinical Features) | Inheritance | Genetic Mutation | Prevalence |
|---|---|---|---|---|
| Classic | Significant skin hyperextensibility and velvety skin.<br>Significant tissue fragility and widened atrophic scars; and/or<br>Significant joint hypermobility. | Autosomal dominant | Type V collagen genes *COL5A1 COL5A2* | 1 in 20 000 |
| Hypermobile | Significant joint hypermobility.<br>Moderate skin hyperextensibility and/or velvety skin.<br>(No significant tissue fragility or wound healing abnormalities.) | Autosomal dominant | Unknown for most cases | 1 in 5000 to 20 000; >90% are female |
| Vascular | Fragility or spontaneous rupture of vasculature or visceral organs.<br>Significant bruising.<br>Thin, translucent skin.<br>Characteristic facies of prominent eyes, thin face, nose, and lobeless ears.<br>(No significant skin hyperextensibility. Joint hypermobility restricted to minor joints.) | Autosomal dominant | Type III collagen gene *COL3A1* | 1 in 50 000 to 100 000 |
| Kyphoscoliotic | Significant joint hypermobility.<br>Severe muscular hypotonia at birth.<br>Progressive kyphoscoliosis.<br>Globe rupture. | Autosomal recessive | Collagen lysyl hydroxylase | Rare |
| Arthrochalasic | Severe joint hypermobility with recurrent subluxations.<br>Congenital bilateral hip dislocation.<br>(Moderate skin hyperextensibility and tissue fragility.) | Autosomal dominant | Type I collagen genes *COL1A1* and *COL1A2* | Rare |
| Dermatosparactic | Severe skin fragility.<br>Sagging and redundant skin.<br>(Easy bruising and soft, doughy skin) | Autosomal recessive | Procollagen I N-terminal proteinase (*ADAMST2* gene) | Rare |

[a] Data are from Steinmann et al,[1] Beighton et al,[11] and Christophersen and Adams.[12]

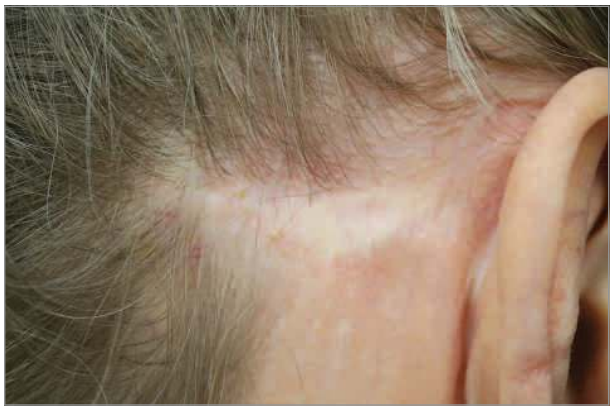
erated from these queries were reviewed for relevance, and pertinent publications were selected for inclusion in this review. The bibliographies of selected publications were reviewed, based on which supplementary searches were also performed. A total of 37 publications were selected to compile this review.

## Discussion

### Pathophysiologic Characteristics

Ehlers-Danlos syndromes are most commonly caused by genetic mutations affecting fibrillary collagens, including type I, III, and V collagen (**Table 1**). The mutations result in qualitatively aberrant collagen that have small or more variable bundle size.[13] In the skin, the collagen fiber bundles are less tightly packed and have a disorderly arrangement with a whorled appearance on histologic examination.[13,14] This disorganization underlies the loss of skin biomechanical integrity. Ehlers-Danlos syndromes can also affect numerous other organ systems in which collagen is present, including the ligaments and joints, the gastrointestinal tract, and blood vessels.[15] One of the most serious potential complications of EDSs is severe bleeding, especially seen in vascular EDS. These patients have a median life expectancy of 48 years, with the most common cause of death being arterial rupture.[16] The genetic defect for vascular EDS is type III collagen, which is a main component of major blood vessels. The total collagen content in the arterial vasculature is markedly reduced, resulting in attenuated vascular walls.[17,18] Furthermore, while coagulation test results for clotting factors and bleeding time are usually within normal limits, some evidence suggests that platelets have decreased ability to aggregate in response to collage in patients with EDSs.[14,19]

Figure 1. Widened Face-lift Scar



Widened face-lift scar after scar revision in a patient with classic type Ehlers-Danlos syndrome.

### Clinical Presentation to the Facial Plastic Surgeon

Patients with EDSs often develop premature facial aging, with significant soft-tissue laxity resulting in redundancy in facial and periocular skin. The facial rhytids in these patients can be irregular, with both horizontal and vertical orientation, forming a reticular pattern.[1] Furthermore, a history of mechanical falls due to joint hypermobility and instability may result in traumatic nasal deformities as well as irregular and poorly healed scars of the forehead and chin.[20] The scars of patients with EDSs tend to be widened, have a "cigarette-paper" appearance, and can be hyperpigmented (**Figure 1**).[1] Finally, patients with certain EDS subtypes have characteristic facies

Figure 2. Characteristics of Ehlers-Danlos Syndrome (EDS)


A an B, Excessive skin laxity (stretchable) noted on the dorsum of the hand and the neck skin in a patient with EDS. C, Joint hyperextensibility exhibited at the proximal interphalangeal joint. These maneuvers can be used as part of a screening assessment for patients with EDS.

that include lobeless ears, epicanthal folds, prominent eyes, or telecanthus and widened nasal bridge with age (Table 1).[20] Patients with EDS are often dissatisfied with their appearance for these reasons,[10] prompting them to seek facial plastic surgery consultation.

## Assessment and Diagnosis

If an EDS is suspected, a detailed history should be obtained with specific questions about joint hypermobility (eg, dislocations or subluxations), easy bruising or bleeding (eg, following teeth brushing or dental extraction), poor wound healing (eg, severe scarring), or gastrointestinal tract issues (eg, hiatal hernia, anal prolapse).[1] Family history is important because most subtypes of EDSs are inherited in an autosomal dominant pattern. Sample screening questions that cover the most important aspects of EDSs can be remembered with the mnemonic E(hlers) DANLOS S(yndromes), and include: *E*xtensible skin ("Is the skin on the back of your hand or forearm exceptionally stretchable?"); *D*ouble jointed ("Are you double jointed?"); *A*rm bending ("Can you bend your thumb to your forearm or do you have exceptional bending of your arm at the elbow?"); *N*odules ("Do you have any nodules that form over your elbows or knees?"); *L*axity of joints ("Did you have more than one joint dislocation as a child or teenager?"); *O*dd body positions ("Can you perform body contortions or do splits?"); *S*carring ("Do you have significant scarring from prior injuries?"); *S*iblings ("Do you have any siblings or other family members with a diagnosis of EDS?"). These questions are not meant to be a validated diagnostic instrument, but may assist the facial plastic surgeon with eliciting medical history or physical examination features suggestive of EDSs.

Physical examination to screen for EDSs by the facial plastic surgeon should focus on the skin and joints. Skin hyperextensibility should be tested by pulling the skin on the volar surface of the forearm, dorsum of the hand and/or neck (**Figure 2**A and B). The skin is stretched until resistance is encountered, and then the distended skin is observed to snap back.[1] The skin is noted to be more "stretchy" and hyperelastic than that of patients without EDSs. The skin of these patients tends to be white, fragile, thin, and velvety to the touch.[1] Significant rhytids are often seen in the face and hands. Wide, atrophic, and sometimes hyperpigmented scars are seen on body sites subject to frequent mechanical trauma (eg, forehead, chin, elbows, or knees).[1] Subcutaneous nodular lesions (molluscoid pseudotumors or spheroids) may also form over these areas.[21] Joint hypermobility can be assessed at the elbows, knees, trunk, and hands using the criteria of Beighton et al,[11] whereby a score of 5 or greater out of 9 defines hypermobility in adults younger than 50 years (**Table 2**).[22] Joint laxity can be assessed by noting if the patient can touch their thumb to their forearm or dorsiflex the fifth finger beyond 90° (Figure 2C).

Ehlers-Danlos syndromes are typically diagnosed based on clinical findings and family history. Nevertheless, genetic consultation should be considered in certain patients: patients older than 4 years and with family history positive for EDS, Beighton score greater than or equal to 5, history of recurrent dislocations with minor trauma, recurrent postoperative instability, and personal or family history of arterial or visceral rupture.[23] Geneticists will make the diagnosis and subtype classification[11] (Table 1). Timely diagnosis of EDS is essential before initiating the appropriate care of these patients, including genetic counseling for patients and families, musculoskeletal treatment, cardiovascular screening (for valvular and vascular abnormalities), and optimizing perioperative treatment.

## Treatment

There is no medical therapy that can cure EDSs.[1] The treatment of patients with EDSs primarily entails preventing, monitoring, and treating EDS-associated complications. For the facial plastic and reconstructive surgeon, treatment of these patients should be individualized based on the patient's chief concern, manifestations, and subtype of EDS. Herein, we discuss recommendations in treatment of patients with EDSs for facial plastic surgeons.

### Preoperative Considerations

When evaluating a patient with a suspected or diagnosed EDS for potential facial plastic surgery, it is important to first determine the subtype of EDS and the severity of EDS-related manifestations. A genetic consultation will provide guidance in diagnosis and in predicting potential surgical complications. All subtypes of EDS carry some increased risk of poor wound healing, abnormal scarring, and bleeding complications, but vascular EDS carries the greatest risk for severe bleeding and anesthesia complications.[14,24] Therefore, elective surgery should be avoided in patients with vascular EDS.

Table 2. The Beighton Scale for Assessing Joint Hypermobility in Patients With Ehlers-Danlos Syndromes[a]

| Clinical Finding | Points |
|---|---|
| Passive apposition of the thumb to the flexor aspect of the forearm | 2 (1 point for each thumb) |
| Passive dorsiflexion of the fifth finger beyond 90° with the forearm flat on a table | 2 (1 point for each fifth finger) |
| Hyperextension of the elbow beyond 10° | 2 (1 point for each elbow) |
| Hyperextension of the knee beyond 10° | 2 (1 point for each knee) |
| Forward flexion of the trunk with the knees extended while the palms rest flat on the floor | 1 |

[a] Data are from Beighton et al.[11]

It is imperative to properly manage these patients' expectations about the range of possible outcomes of facial plastic surgery. A thorough and individualized discussion should be held about EDS-specific risks. The degree of scarring a patient already has can help predict the amount of tissue fragility to be encountered intraoperatively.[1] Patients should also be informed that while scar revision can often improve the appearance of scars in individuals without EDS, these procedures commonly result in similarly widened scars in those with EDSs (Figure 1).[25]

With the exception of traumatic soft-tissue injury, alternative nonoperative and noninvasive therapies should be discussed and considered first. For example, pulsed carbon dioxide laser, and carbon dioxide–Er:YAG laser have been used successfully in lieu of blepharoplasty for patients with EDS without complications and with satisfactory outcome.[26] When surgical intervention is elected or required, conservative and minimally invasive approaches should be used.

All patients with EDSs who elect to proceed with surgery should receive preoperative clearance, preferably at a specialized preoperative evaluation center, which should include a cardiovascular survey with an echocardiogram.[23,27] Patients with mitral valve regurgitation may require antibiotic prophylaxis. Given the propensity of these patients to have uncontrolled bleeding, blood type and crossmatch testing should be performed as well as tests to ensure that no concomitant coagulopathy exist.[27]

### Anesthetic Considerations

It is important for the facial plastic surgeon to alert the anesthesiologist of an EDS diagnosis preoperatively. Clinically significant anesthesia-related complications have been reported for patients with EDSs, including cervical spine, craniocervical, and mandibular instability, and skin trauma during intubation, joint dislocation during positioning, excessive bleeding, and hematoma formation owing to vascular access placement, spontaneous pneumothorax, collapse of upper airway, tracheal rupture, spontaneous vascular dissection, and arterial rupture.[14,27-30] While some believe that anesthesia may be performed safely with standard techniques without special precautions,[29] anesthesiologists must be aware of the diagnosis so that all interventions can be performed with utmost care with preference given to conservative measures.

### Intraoperative Considerations

Numerous surgical complications have been reported to occur for patients with EDSs as a result of the fragility of their vessels and tissue.[2-7] It has been observed that the initial surgical incision may widen spontaneously, and deep tissue can "fall apart at the touch of a blade."[20] Therefore, tissue must be handled with extreme care, and use of skin retractors and dissection should be minimized. Because of the vascular fragility, meticulous hemostasis must be maintained throughout a procedure. Electrical cautery may be helpful,[20] but vessel loops and clamps should be avoided because they can cause vessel injuries that are difficult to repair.[1,30,31] Primary arterial repair is challenging owing to poor tensile strength of the vessels, but can be achieved with interrupted horizontal mattress sutures reinforced with pledgets.[1,31]

Wound dehiscence is one of the most common complications in all subtypes of EDSs and can occur from days to years following the original surgery.[32] To reduce the risk of dehiscence, wound closure should be performed meticulously. This may be challenging because the sutures have been observed to tear out of the fragile tissues, preventing good apposition of the wound edges.[20] Techniques that have been reported to have good outcome include generous use of deep sutures; layered closure of wound to minimize tension; use of Steri-strips (3M) or other adhesive tapes to further reduce tension on wound edges; and avoiding traumatizing skin edges by grasping with instruments, tearing the skin with retracting hooks, and the use of skin staples for wound closure.[7,30]

### Postoperative Considerations

Postoperatively, wounds should be observed closely for the development of dehiscence, infection, or hematoma. If nonabsorbable sutures are used, they should remain in place for approximately twice as long as normal.[33,34] The removal of any Steri-strips or other adhesive tapes should be performed with care. Any wound dehiscence can increase the risk of infection, which has been reported to be up to 6 times higher than normal in patients with EDSs.[7] Anticoagulation should be used with caution given the increased risk of bleeding and hematoma formation. Options for postoperative scar management are also limited because these patients are at higher risk for atrophy or cyst enlargement after intralesional steroid injection.[9]

### Considerations for Specific Facial Plastic Surgical Procedures

**Rhytidectomy and Blepharoplasty** | To our knowledge, only 3 reports of rhytidectomy for patients with EDSs exist in the literature.[26,35,36] Guerrerosantos and Dicksheet[35] performed rhytidectomy on a patient with EDS of unknown subtype in 1985. They encountered extreme tissue fragility and hemorrhage that was difficult to control with electrocautery and suture ligature, such that superficial musculoaponeurotic system plication could not be performed.[35] The postoperative course was complicated by 3 separate episodes of hematomas requiring drainage, and a retroauricular wound dehiscence occurred.[35] In a separate report, Mueller et al[26] described a patient with class type EDS who had undergone 2 conventional face-lifts and blepharoplasties without any reported complications, but with unsatisfying results, even in the immediate postoperative period, owing to residual redundant skin. Most recently, Rollet et al[36] reported an uncomplicated rhytidectomy on a patient with classic type EDS. They performed a modification of the minimal access cranial suspension face-lift with no undermining in the subcutaneous tissue plane. They used many of the surgical tech-

niques recommended in this review, including using absorbable sutures throughout the procedure, layered wound closure, and supporting the wound with Steri-strips and a compression dressing for the night of surgery. This patient reportedly had an uneventful recovery and a satisfactory outcome.[36]

Taken together, these reports suggest that while some patients with EDS develop severe surgical complications, others may undergo rhytidectomy and blepharoplasty without issues. This is likely in part related to the phenotypic heterogeneity of the various subtypes of EDS. We consider vascular EDS to be a contraindication for elective surgery given the potential for life-threatening consequences. For patients with nonvascular subtype EDS, it is important to understand that not having surgical complications does not guarantee a satisfactory outcome, as seen in the case described by Mueller and colleagues.[26] Interestingly, this patient subsequently underwent 2 full-face laser skin resurfacing procedures with pulsed carbon dioxide laser and carbon dioxide–Er:YAG laser over a period of 9 months, with uncomplicated healing and a marked improvement in facial appearance.[26] This underscores the importance of managing patient expectations preoperatively and the consideration of alternative non-operative and non-invasive options.[26]

**Rhinoplasty** | To our knowledge, there are no reports in the literature on rhinoplasty in patients with EDSs. Nonetheless, these patients often have traumatic nasal deformities from repetitive falls owing to joint instability and may present for facial plastic surgery evaluation.[20] There do not seem to be absolute contraindications for most patients with EDSs to undergo rhinoplasty. The potential for widened scars and wound dehiscence may support the use of endonasal rhinoplasty approaches to avoid poor healing of a columellar incision. Extreme care should be taken during elevation of the skin–soft-tissue envelope to avoid shearing of the flap with retracting hooks, and the skin may be more delicate than in typical noses. The nasal septal cartilage and lobular cartilage are composed primarily of type II collagen, which is not typically affected in EDS.[37] Therefore, one should be able to proceed with procedures on the nasal cartilages in a typical fashion. Septal cartilage harvest should still be carried out with caution, and multiple approaches to prevent hematoma formation should be used, such as splints, quilting sutures, and possibly fibrin glue.

**Reconstruction With Grafts and Flaps** | The successful use of split-thickness skin grafts in patients with EDS has been reported for lower extremity wounds.[32,38] The Reese dermatome was felt to be less traumatic compared with electric or pneumatic dermatomes.[30,32] Humby knife may be difficult to use for harvest of skin grafts owing to skin laxity and can result in inadvertent full-thickness incisions through the dermis.[38] Interestingly, there seems to be less skin graft contraction (7%) in patients with EDSs compared with those without EDSs (10%).[38] Wesley et al[30] described a technique of applying Benzoin to the edges of the skin graft and use of Steri-Strips to avoid use of sutures.

There is only 1 report of the use of free flap in patients with EDS. Creasy et al[39] described an uneventful experience performing bilateral deep inferior epigastric perforators flaps for breast reconstruction in a patient with classic-type EDS.[39] These authors felt that classic EDS was not a contraindication to microsurgical surgery, but recommended that patients with EDSs be considered on a case by case basis. To our knowledge, no reports of free tissue transfer performed in the head and neck region exist.

## Prognosis

There is no cure for EDSs. The prognosis for patients with EDSs undergoing surgery depends largely on the subtype and severity of EDS. Whereas many patients with classic type EDS can undergo facial plastic surgery without major intraoperative complications,[26,36] they may still develop postoperative complications, such as wound dehiscence or suboptimal scar appearance. Patients with vascular EDS are at high risk for both intraoperative and postoperative complications with poor prognosis, and elective surgery should be avoided in these patients.[14,27-30,40]

## Conclusions

Patients with EDS often seek consultation with the facial plastic surgeon for undesired facial features, such as excessive rhytids, skin laxity, or excessive scarring. It is important for the facial plastic surgeon to recognize signs of EDS and, if appropriate, refer these patients for genetic consultation for diagnosis and classification. Understanding the severity and subtype of EDS greatly facilitates proper management of expectations for both the surgeon and patients. In this review, we provide essential preoperative, intraoperative, and postoperative considerations to guide the facial plastic surgeon in providing individualized and optimal care for patients with the EDSs.

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