

# Disorders Leading to Early-Onset Osteoarthritis: Orthopedic Considerations and Insights

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## ABSTRACT

Osteoarthritis (OA), characterized by articular cartilage deterioration, is influenced by factors such as age, trauma, genetic alterations, and inflammatory diseases. Early-onset osteoarthritis (EO-OA), typically observed before 40 or 50, can result from genetic mutations affecting connective tissue, inflammatory diseases, or trauma. Genetic syndromes like pseudoachondroplasia or spondyloepiphyseal dysplasia, along with mutations in collagen genes contribute to early-onset OA development.

Disorders like spondyloepiphyseal dysplasia and multiple epiphyseal dysplasia manifest with skeletal anomalies and joint issues, necessitating careful orthopedic management. In conditions like achondroplasia and Stickler syndrome, EO-OA arises due to axis and shape abnormalities rather than primary cartilage problems. Hemophilic arthropathy, characterized by recurrent intra-articular bleeding, requires prophylactic measures and meticulous perioperative management during joint replacement surgeries. Alkaptonuria and chondrocalcinosis lead to cartilage degeneration and tissue damage, requiring caution during orthopedic interventions. Inflammatory arthritis, particularly rheumatoid arthritis and ankylosing spondylitis, elevates complication rates post-arthroplasty. Ehlers–Danlos syndrome (EDS) poses challenges due to tissue fragility and laxity, demanding careful surgical techniques and postoperative care.

Each disorder presents unique challenges in orthopedic management, ranging from joint instability to increased infection risks. Patient-specific factors, including genetic predisposition and systemic complications, influence surgical outcomes and implant survival rates. Orthopedic surgeons must tailor interventions to address underlying pathology while minimizing risks associated with each disorder, ensuring optimal patient outcomes and satisfaction.

**Keywords:** Achondroplasia, alkaptonuria, collagen, dysplasia, early onset, Ehlers–Danlos, gonarthrosis, hemophilia, knee, osteoarthritis, surgery

## INTRODUCTION

Osteoarthritis (OA) is recognized as the most common joint disorder globally, particularly impacting the knees, hips, spine, hands, and feet, characterized by the gradual deterioration of articular cartilage.<sup>1,2</sup> In OA, not only the joint cartilage undergoes changes, but also encompassing tissues, including the synovium, subchondral bone, joint capsule, ligaments, periarticular muscles, and nerves are affected.<sup>3</sup> The development of OA is influenced by various key factors, including advanced age, female gender, trauma, joint imbalance, muscle laxity, occupational conditions that induce repetitive stress on specific joints, metabolic disorders, inflammatory diseases like

rheumatoid arthritis, bone deformities, and genetic alterations. These factors play crucial roles in the onset of OA.<sup>4</sup> Cases without a clearly identified predisposing factor are classified as primary idiopathic, whereas cases with discernible factors are categorized as secondary.<sup>2</sup>

Idiopathic OA represents the most common form of arthritis, with reports indicating that 60% of males and 70% of females aged 65 and above suffer from this condition.<sup>5</sup> Although OA is predominantly a disease affecting the elderly, it can occasionally manifest at earlier ages. Cases of osteoarthritis observed typically before the age of 40 or 50 are categorized as early-onset OA (EO-OA).<sup>6</sup> This review explores genetic alterations and

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diseases that contribute to the development of EO-OA (Table 1).

Early-onset osteoarthritis often arises due to secondary causes. Various genetic mutations affecting connective tissue, inflammatory diseases, hemophilia, or excessive biomechanical disruption following trauma contribute to its development. Idiopathic EO-OAs are relatively rare, yet they may exhibit mutations similar to those associated with genetic syndromes in EO-OAs.<sup>7</sup>

Development of EO-OAs with a genetic basis may manifest as part of a genetic syndrome, such as pseudoachondroplasia or spondyloepiphyseal dysplasia, or may arise due to mutations in extracellular matrix proteins, transforming growth factor pathways, and proteins involved in bone modeling, without being associated with a specific syndrome.<sup>7</sup>

In either syndromic or idiopathic EO-OAs, the most frequently observed common alteration is mutations in genes that encode collagen proteins. Collagens, produced by chondrocytes, constitute a protein family forming the main structural components of the extracellular matrix.<sup>8</sup>

The primary collagens of articular cartilage are types II, XI, and IX, with collagen type II representing 80% of all. It serves as the principal structural component of hyaline cartilage on joint surfaces and is also found in tissues such as the retina, sclera, lens of the eye, intervertebral discs, and nucleus pulposus.<sup>9</sup> The type II collagen (COL) chain contains tripeptide sequences with glycine occurring every third fold. Most mutations in the *COL2A1* gene, which is responsible for encoding type II collagen, result in the substitution of glycine with serine, an amino acid characterized by a larger molecular size.<sup>10</sup> Mutations that cause amino acid changes can disrupt protein stability

and helical structure, leading to alterations in collagen function.<sup>11</sup>

Abnormal collagen synthesis results in a reduced number of collagen fibrils in the cartilage growth plate matrix. COL2A1 mutations can give rise to a range of disorders, from relatively mild, late-onset spondyloepiphyseal dysplasia to perinatal lethal achondrogenesis type II. The phenotypic features of the disease are associated with a decrease in the number of collagen fibrils.<sup>12</sup>

Hypochondrogenesis, Strudwick, Kniest, and Stickler dysplasia are Spondyloepiphyseal dysplasias that result from mutations in the *COL2A1* gene. In these syndromes, in addition to EO-OA, changes are observed in tissues containing type II collagen, such as the retina, sclera, lens of the eye, intervertebral discs, and nucleus pulposus.<sup>13</sup> Therefore, type II collagenopathies manifest various clinical findings at different levels, depending on the severity of the disease and the involvement of distinct areas.<sup>14</sup>

The type of mutation in the *COL2A1* gene is crucial concerning the prevalence, severity, and course of the disease. It is known that distinct mutations unrelated to spondyloepiphyseal dysplasia, Stickler syndrome, or congenital cartilage anomalies can also cause EO-OA.<sup>15-17</sup> Identified *COL2A1* mutations and associated diseases are summarized in Table 1. Determining the presence and type of mutation can provide insights into the course of the disease.

In addition to type II collagen, another collagen present in articular cartilage is type IX collagen. It is mainly found in the growth plate, adult joints, and intervertebral discs. This collagen contributes to the stabilization of the fibrillar network in the cartilage matrix and regulates the diameter of collagen fibers by facilitating the binding of matrilin 3 and proteoglycans.<sup>18</sup>

Type IX collagen is essential for the stability of articular cartilage. Disruptions in the structure of this collagen lead to conditions such as multiple epiphyseal dysplasia (MED) and certain skeletal anomalies, which lead to osteoarthritis affecting the knee joint.<sup>19,20</sup>

Clinical features vary based on mutations observed in type IX collagen and the affected chain, as outlined in Table 2. Additionally, isolated mutations in *COL9A1*, *COL9A2*, and *COL9A3* have been reported in idiopathic EO-OA.<sup>6,21,22</sup>

Collagen type XI is one of the minor collagens in articular cartilage. It possesses a heterodimeric structure formed by the combination of proteins encoded by three separate gene regions. It forms a polymer with type II and IX collagens in the cartilage.<sup>23</sup> Mutations in type XI collagen are associated with conditions such as autosomal recessive

## MAIN POINTS

- Early-onset osteoarthritis can result from genetic mutations affecting connective tissue, inflammatory diseases, or trauma.
- Spondyloepiphyseal dysplasia, multiple epiphyseal dysplasia, achondroplasia and Stickler syndrome manifest with skeletal axis and shape anomalies. Hemophilia causes recurrent intra-articular bleeding that leads to joint destruction. Alkaptonuria and chondrocalcinosis lead to cartilage degeneration and tissue damage. Ehlers-Danlos syndrome poses challenges due to tissue fragility and laxity. Inflammatory arthritis elevates complication rates post-arthroplasty.
- Each disorder presents unique challenges in orthopedic management, ranging from joint instability to increased infection risks.

**Table 1.** Mutations in the COL2A1 Gene Encoding Type II Collagen and Associated Diseases

Gene	Production	Mutation	Related Diseases
COL2A1	Tip-II collagen, $\alpha 1$	12q12–q13.2	Familial EO-OA Avascular necrosis of femoral head Legg–Calvé–Perthes Czech dysplasia Kniest dysplasia Otospondylomegaepiphyseal dysplasia Spondyloepiphyseal dysplasia Stickler syndrome, type I
		12q12–q13.2 c.823C>T (p.Arg275Cys)	Familial EO-OA Age: 12–40 characterized by bilateral involvement of the hip and/or knee joints.
		12q12–q13.2 c.2155C>T (p.Arg719Cys)	Familial generalized EO-OA Age: 20–30 It affects multiple joints, characterized by involvement of the hip, knee, shoulder, wrist, and finger joints.
		12q12–q13.2 c.2659G>A	Familial EO-OA Age: 30–50 characterized by simultaneous involvement of bilateral hip, knee, and elbow joints.

otospondylomegaepiphyseal dysplasia (OSMED), Robin sequence, and non-ocular Stickler syndrome. Isolated mutations in collagen type XI have also been reported in idiopathic EO-OA. Table 3 summarizes COL11A mutations and associated diseases.<sup>6,23</sup>

Another crucial component of the extracellular matrix is proteoglycans. The aggrecan gene (ACAN) encodes aggrecan, the most abundant proteoglycan in cartilage. Its primary function is to provide resistance against

compression, thereby safeguarding bones and joints. While cases of ACAN mutations have been observed in syndromic EO-OA, the direct relationship between ACAN gene mutations and EO-OA remains inconclusive.<sup>24,25</sup> The prevailing consensus suggests that ACAN mutations are not directly linked to the development of EO-OA but play a role in osteoarthritis by causing skeletal anomalies.<sup>6</sup> The protein matrilin 3 is involved in the structuring of the collagen network, acting as a connector between cells. This protein is encoded by the Matrilin-3 (MATN-3) gene.

**Table 2.** Mutations in the COL9A gene encoding collagen IX and Associated Diseases

Gene	Production	Mutation	Diseases
COL9A1	collagen type IX, $\alpha 1$	6q13	Multiple epiphyseal dysplasia, type VI Stickler syndrome, type IV
COL9A2	collagen type IX, $\alpha 2$	1p33–p32	Multiple epiphyseal dysplasia, type II Stickler syndrome, type V
COL9A3	collagen type IX, $\alpha 3$	20q13.3	Multiple epiphyseal dysplasia, type III Stickler syndrome

**Table 3.** Mutations in the COL11A Gene Encoding Collagen Type XI and Associated Diseases

Gene	Production	Mutation	Diseases
COL11A1	collagen type XI, $\alpha 1$	1p21	Stickler syndrome, type II
COL11A2	collagen type XI, $\alpha 2$	6p21.3	Familial EO-OA Stickler syndrome, type III Otospondylomegaepiphyseal dysplasia
COL11A2	collagen type XI, $\alpha 2$	6p21.3 c.1615C>T (p.Arg539Trp)	Familial EO-OA Age: 35–50 Symmetric polyarticular arthritis, hip, knee, shoulder

**Table 4.** Mutations in Genes Encoding Other Components of Cartilage Extracellular Matrix

Gene	Production	Mutation	Diseases
ACAN	Aggrecan	15q26.1	Osteochondritis dissecans Spondyloepiphyseal dysplasia, Kimberley type
COMP	Cartilage oligomeric matrix protein	19p13.1	Familial EO-OA Multiple epiphyseal dysplasia, Type I Pseudoachondroplasia
COMP	Cartilage oligomeric matrix protein	19p13.1 2152C>T (p.Arg718Trp)	Familial EO-OA Age: 16-30 OA like involvement
MATN3	Matrilin 3	2p24–p23	Multiple epiphyseal dysplasia, Type V

Mutations in the matrilin 3 gene result in the misfolding of the MATN-3 protein, leading to its accumulation in the endoplasmic reticulum and causing destabilization in the cartilage tissue.<sup>26</sup> These gene mutations have been shown to be associated with MED.<sup>27</sup> The cartilage oligomeric matrix protein gene (COMP) encodes a pentameric extracellular matrix glycoprotein that catalyzes collagen assembly and supports fibril formation.<sup>28</sup> It contributes to the structural integrity of cartilage. Mutations in the COMP gene have been identified in familial and sporadic pseudoachondroplasias, as well as sporadic MED.<sup>28,29</sup> Additionally, studies in mice have demonstrated that COMP gene deletions result in findings highly similar to pseudoachondroplasia.<sup>30</sup>

The mutations in genes encoding both collagenous components and extracellular matrix proteins of the cartilage lead to structural impairments in the joint cartilage. This condition often results in the clinical manifestation of EO-OA.

According to the literature, patients with gonarthrosis related to skeletal dysplasia typically undergo arthroplasty at an average age of 41, with a mean age for revision surgery being 44.<sup>31</sup> Implant survival rates are lower in these patients compared to healthy individuals. Osteoporosis at a young age is common in this population. Detection and management of osteoporosis should be performed in the preoperative period, as undesirable fractures may occur during arthroplasty surgery.<sup>31</sup> Syndromic phenotypes inherently carry surgical and anesthetic risks. They often involve facial and mandibular issues, cleft palate, micrognathia, and atypical appearance, making intubation challenging. Phenotypes associated with dwarfism may display anomalies in the rib cage potentially compromising pulmonary capacity. In instances where joint laxity is evident, it is important to consider the possibility of atlanto-axial instability. Phenotypes associated with spinal involvement may have stenosis or sclerosis of the discs, which can pose challenges and complicate spinal anesthesia. Soft tissue fragility is increased in collagen tissue disorders, raising the risk of vascular injury and bleeding.

**Spondyloepiphyseal Dysplasia**

Spondyloepiphyseal dysplasia (SED) is a rare disorder characterized by a defect in the synthesis of type 2 collagen, affecting the vertebrae and epiphyses, resulting in disproportionate dwarfism. There are two types: SED congenita, which manifests at birth and is more severe, and X-linked recessive SED tarda, which appears normal at birth, but symptoms emerge as the child grows, predominantly in males. Early-onset osteoarthritis is more common in these patients, particularly in the hips and knees.

Spondyloepiphyseal dysplasia patients frequently exhibit axial deformities, bone deformities, ligament laxities, or soft tissue contractures. Bone diameter is reduced, and muscle–bone orientation may deviate from the normal anatomy. Attention should be paid to these factors during arthroplasty surgery. If instability is present in the knee joint, the use of constrained or hinged prosthetics is advisable. Trochlear groove depth may be shallow, and deviations in Q angle due to short stature and axis deviation predispose these patients to patellar dislocation.<sup>32</sup>

In literature, post-arthroplasty peroneal nerve issues have been described as common in SED cases. Atlanto-axial instability can occur in SED patients, necessitating caution during anesthesia and intubation. Dysplasia in the thoracic bones is also present in these patients, potentially leading to respiratory difficulties.<sup>32,33</sup>

**Multiple Epiphyseal Dysplasia**

Multiple epiphyseal dysplasia is a genetic disorder group involving anomalies in the epiphyses demonstrating autosomal dominant or recessive inheritance through six different genes. There is a disruption in endochondral ossification in the epiphyses of long bones, leading to weak bone support, causing initially normal joints to rapidly progress to osteoarthritis. Although the phenotype varies widely, severe cases may present with dwarfism and finger shortening. It differs from spondyloepiphyseal dysplasia by the absence of spinal involvement, and

facial features remain normal.<sup>34</sup> All joints, particularly the lower extremities, can be affected. While hip issues are more common, significant involvement of the knees is not uncommon. Most patients appear normal in childhood with mild short stature, and symptoms become apparent towards adolescence. Early fatigue, joint pains, and joint contractures may be initial manifestations. Hip x-rays may resemble Perthes disease, but pathology in MED patients is almost always symmetric. Double-layered patella due to two unfused ossification centers can be observed in lateral knee x-rays, and this finding is pathognomonic. Epiphyseal irregularities, segmentations, joint space widening, and genu valgum deformities become prominent in childhood. After epiphyseal closure, the most characteristic feature is the shallow femoral trochlear groove. Joint issues begin to manifest in the 20s in these patients. The lateral tibial plateau has collapsed, joint surfaces are irregular, joint mice are seen, and the knees are in valgus. Some mild cases may have knee morphology close to normal, yet EO-OA can still occur.<sup>34,35</sup> Surgical release of joint contractures, supracondylar extension osteotomy, and physiotherapy are indicated if present. In cases of severe alignment disorders at an early age, corrective osteotomies can delay the progression to osteoarthritis, along with weight control and activity restriction. Epiphysiodesis may be performed in cases of leg length discrepancy to reduce alignment issues during future arthroplasty surgery.<sup>36</sup>

### Achondroplasia

Achondroplasia is the most common skeletal dysplasia caused by fibroblast growth factor receptor disorder, leading to short limbs and dwarfism with autosomal dominant inheritance. The trunk is elongated, especially the proximal long bones are short, resulting in rhizomelic dwarfism. There is mild macrocephaly with frontal bossing and mid-face hypoplasia. Trident hand and, particularly, joint laxity in the knees are observed. Spinal stenosis may be present. The genetic defect in achondroplasia does not affect cartilage health, so the development of osteoarthritis is more related to axis and shape abnormalities than primary cartilage problems. Joint space is widened, metaphyses have angulation. Varus is often present due to distal femoral varus and lateral tibial bowing, aggravated by joint laxity. Flexion contracture is common in the knees, tibial slope is decreased, potentially causing genu recurvatum. Abnormal gait dynamics accelerate osteoarthritis development.<sup>37,38</sup> Consequently, advanced-stage osteoarthritis can rarely be observed at an early age. To delay osteoarthritis development, alignment surgeries and braces or knee orthoses for joint laxity may be recommended. When arthroplasty is required, standard measurement and cutting tools may not be suitable for these patients. Custom-made prosthetics and computer-assisted robotic cutting

methods are advised. In cases where these are unavailable, manual cutting is performed based on visual estimation. Due to the potential difficulty in achieving soft tissue balance related to ligament laxity, constrained or hinged prosthetics, augmentations for extra bone cuts, and components with stems to enhance bone integration and ensure proper alignment should be available.<sup>31,37-38</sup>

### Stickler Syndrome

In Stickler syndrome, the major manifestation is EO-OA, with involvement in all joints, including the vertebrae. Genetic changes result in various degrees of problems such as long limbs, long fingers, enlarged joints, genu valgum, joint laxity, muscle hypotonia, osteoporosis, severe myopia, and hearing problems. Following the development of arthrosis, joint hypermobility gives way to contractures. Most patients require arthroplasty before the age of 40. Intubation issues during anesthesia may arise due to mandibular problems and micrognathia. Muscle hypotonia, hearing and vision impairments may hinder these patients from being self-sufficient during the rehabilitation period. Therefore, a program under the guidance of a physiotherapist would be appropriate.<sup>39</sup>

### Hemophilic Arthropathy

Hemophilic arthropathy is an X-linked hereditary bleeding disorder resulting from a deficiency in factor 8 or 9. Bleeding attacks occur in large joints. Depending on the severity of factor deficiency, it can lead to dozens of intra-articular bleeding episodes within a year. Excessive iron resulting from erythrocyte breakdown causes damage to the joint cartilage and synovium. Recurrent bleeding causes synovitis, and synovial hypertrophy progresses into scar tissue which causes joint contractures. In children and adolescents, the ankle is more often affected, whereas in adults, the knee is the most commonly affected joint. Hemophilia patients typically need total knee arthroplasty between the ages of 38 and 44. The most effective preventive measure involves reducing the frequency of intra-articular bleeding through suitable prophylaxis. In cases of recurrent hemarthrosis in a single joint, chemical, radiotherapeutic, or surgical synovectomy to prevent inflammation will buy time for the patient.

During acute hemophilic hemarthrosis attacks, in addition to immediate factor replacement in subsequent hours, rest, ice, elevation, and compression are recommended. After about a week of non-weight-bearing, gradual weight-bearing with crutches is advised. If factor replacement therapy has been performed in the presence of massive hemarthrosis, joint aspiration should be performed as early as possible.<sup>40</sup> Aspirin and its derivatives are not recommended as analgesics; selective cyclooxygenase (COX)-2 non-steroidal anti-inflammatory drugs (NSAIDs) are more suitable. Adequate factor replacement



during the preoperative period significantly prevents bleeding issues, allowing knee replacement surgery to be safely performed. A factor level of 100% is recommended during the preoperative period. Postoperatively, factor 7 should be maintained at 80–100%, and factor 9 at 60–80% for at least 3 days.<sup>41</sup> Considering the potential for excessive bleeding, perioperative bleeding control should be performed more carefully. Surgical procedures are recommended with a tourniquet. The use of tranexamic acid has been shown to reduce bleeding. Hemoglobin levels can drop up to 4 g/dL in the postoperative period, and consequently, red blood cell replacement may be higher than in healthy patients. Drains are removed on the second or third day in the postoperative period.<sup>42,43</sup>

The implant survival rate in patients undergoing total knee arthroplasty due to hemophilic arthropathy is around 81–92% in 10 years, which is similar to healthy individuals. Patient satisfaction is also similar to healthy individuals; however, the flexion range around the joint is generally reduced due to fibrotic contractures of the surrounding ligaments and muscles.<sup>44,45</sup>

Postoperative infection rates have been reported to be up to 10 times higher than in healthy individuals. In many studies, infection rates range from 4 to 17%.<sup>43</sup> It has been found that a high level of coagulation factor replacement in the postoperative period reduces the infection rate. However, this approach also increases the risk of deep vein thrombosis. Nevertheless, in these patients, thromboprophylaxis should be provided by mechanical methods, and the use of factor inhibitors should be avoided. Considering that infections transmitted from blood products such as human immunodeficiency virus (HIV) and hepatitis C virus (HCV) can be common in hemophilic patients, the surgeon should take appropriate precautions.<sup>41,46</sup>

### Alkaptonuria

Alkaptonuria is an autosomal recessive disorder affecting tyrosine metabolism. Due to a deficiency in homogentisic acid oxidase enzyme, there is deposition of dark-colored homogentisic acid and its oxidized forms in tissues. Typically, in the third or fourth decade, tissues such as the sclera, ear, nails undergo a blue-black color change, and dark-colored urine or sweat becomes evident. Besides causing pigmentation and color change, this pigment also leads to degeneration, inflammation and calcification in tendons, ligaments, intravertebral disks, and large joints, resulting in increased bone destruction. Accumulation of this substance in cartilage tissues renders the tissue more brittle, causing rapid degeneration, known as ochronotic arthropathy. Although the large joints, especially the knee, are commonly affected, in many cases, symptoms are preceded by spinal involvement. There is no definitive treatment for alkaptonuria.

Considering increased cartilage fragility, precautions such as avoiding strenuous activities, sports, weight control, etc., are recommended.<sup>47,48</sup> Patients usually require arthroplasty in their 40s. Cardiovascular involvement is common in these patients. Stenosis and calcifications may be observed. A thorough cardiological evaluation should be performed in the preoperative period. Disk calcifications and narrowed spaces in the vertebrae may hinder spinal interventions, favoring general anesthesia. Tracheal and bronchial cartilages can be sclerotic thereby complicating intubation. If cervical vertebra involvement exists, providing a position for intubation becomes challenging. Abnormal pigment accumulation in the nails can make pulse oximetry measurements unreliable.<sup>49</sup> The outcomes of arthroplasty in these patients are similar to those in healthy individuals.<sup>50</sup>

### Chondrocalcinosis

Pseudo-gout is a disease characterized by the accumulation of calcium pyrophosphate in the pericellular matrix of fibrous and hyaline cartilage and synovial fluid. There are sporadic and familial forms or accompanied by hemochromatosis, hypothyroidism, and Wilson's disease. These crystals have a direct catabolic effect on chondrocytes. Moreover, they cause inflammation and eventually tissue damage by increasing metalloproteinase activation and prostaglandin production. In this condition, osteoarthritis development accelerates. The most commonly affected joints are the knee, wrist, and pubic symphysis.

Clinical outcomes and implant survival rates of total knee arthroplasty (TKA) surgeries performed in chondrocalcinosis patients are similar to healthy individuals. There is no specific consideration mentioned in the literature, but reduced range of motion may be observed in cases of radical synovectomy in advanced chondrocalcinosis, possibly due to recurrent bleeding and fibrosis.<sup>51,52</sup>

### Inflammatory Arthritis

Complication rates after arthroplasty for the development of gonarthrosis on an inflammatory arthritis background are higher than in healthy individuals. However, these rates do not significantly differ based on the type of disease. Patients with inflammatory arthritis have approximately 1.5 times higher infection and revision rates. The likelihood of deep vein thrombosis is especially increased in patients with rheumatoid arthritis and ankylosing spondylitis. These patients often use immunosuppressive and steroid-effect drugs, leading to higher systemic complication rates. Ankylosing spondylitis rarely affects the knee joint. In cases where it does, the range of motion of the knee is generally limited. Although a significant increase in the range of motion is not expected after arthroplasty, pains and functional scores increase significantly. The rate of heterotopic ossification is high.<sup>53</sup>

## Ehlers–Danlos Syndrome

Ehlers–Danlos syndrome (EDS) is a connective tissue disorder with various subtypes, which can have both autosomal dominant and autosomal recessive inheritance, characterized by flexible and fragile skin and soft tissues, and joint laxities. It is encountered at a rate of 1–2/10 000, and it is more common in females.

These patients develop problems related to hypermobility, especially in the hands and ankles. Patellar dislocations and tibiofemoral instability are more common. In the rarer vascular subtype (type 4), which is associated with internal organ and vessel ruptures, life expectancy may be shorter, but most EDS patients live for many years. The vascular type is the riskiest type in terms of serious complications, classical symptoms such as joint laxities and flexible skin are less common in this type. Other types are more prone to EO-OA due to joint laxities. Chronic joint pains are observed in 85% of patients, and approximately 60% experience laxities in the knee joint. Around 40% of these patients need crutches or a wheelchair at some point in their lives.

Due to soft tissue sensitivity and vascular fragility in EDS patients, care should be taken during tissue dissection and retraction in surgery. When removing plasters attached to the skin in wound dressings, they can cause skin tears. The use of a tourniquet can damage tissues. Compressing the trunk with table apparatus during position giving may pose a danger for prone to organ ruptures in this patient population. Aortic, pulmonary, or mitral insufficiencies may be observed in these patients, and preoperative cardiac evaluation should be performed with doppler ultrasonography (USG). During patient transfer, pulling the skin and twisting it while holding the arms and legs can easily tear the skin or cause joint dislocations. Temporomandibular joint dislocation may occur during intubation due to joint laxity. Postural orthostatic tachycardia may be observed, especially in hypermobile type EDS patients. There is no different recommendation for the types and doses of drugs used in the induction of anesthesia in these patients. Central catheterization and arterial procedures are dangerous due to vascular fragility. If necessary, they should not be performed blindly, but with special care under ultrasound guidance. Spinal epidural anesthesia is not recommended in vascular type EDS, but successful cases have been reported. Due to the possibility of esophageal rupture due to intense vomiting and retching in the postoperative period, the use of antiemetics is recommended.<sup>54</sup>

Patient satisfaction rates after TKA in EDS are lower than in healthy individuals. Although functional scores are lower after surgery compared to other cohorts, patients are satisfied with the resolution of instability and reduced

pain. Patellar instabilities in these patients are persistent, so particular attention should be paid to technical details such as component rotation and achieving soft tissue balance to avoid patellar maltracking. Especially, posterior stabilizing prostheses may be preferred to compensate for joint laxity.<sup>55</sup> There is a publication reporting that attempting to correct recurrent varus–valgus instability by implanting thicker inserts gradually initially corrects instability but becomes unsuccessful after a few years. Therefore, the use of a hinged prosthesis better be considered based on the patient's potential for instability.<sup>56</sup> Infection rates are nearly twice as high as in healthy individuals. Sutures can cut through the skin when tightened. Wound healing requires a longer period for suture removal.

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