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Orthopaedic Management of Loeys-Dietz Syndrome: A Systematic Review

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ABSTRACT

Introduction: Loeys-Dietz syndrome (LDS) is an autosomal dominant connective tissue disorder associated with aortic aneurysm/dissection in children. However, LDS may also present with a host of orthopaedic conditions. This study aimed to elucidate the management of orthopaedic conditions and associated outcomes in patients with LDS.

Methods: PubMed, Ovid MEDLINE, and Cochrane Library were systematically searched for primary articles regarding the management of orthopaedic conditions in patients with LDS. The goals and findings of each included study were described. Data regarding demographics, conditions studied, treatment modalities, and outcomes were extracted and analyzed.

Results: Three hundred sixty-two unique articles were retrieved, 13 of which were included, with 4 retrospective cohort studies and 9 case reports representing 435 patients. In total, 19.8% of patients presenting with orthopaedic conditions received surgical treatment;54.3% of them experienced adverse outcomes, and 44.4% required revision surgery. The mean age at surgery was 9.0 ± 2.1 years.

Conclusion: Patients with LDS may require early surgical intervention for a variety of orthopaedic conditions and may be at an increased risk for surgical complications. The current LDS literature is primarily focused on spinal conditions with a relative paucity of data on the management of hip deformity, joint subluxation, clubfoot, and trauma. Additional research is required regarding orthopaedic management for this unique population.

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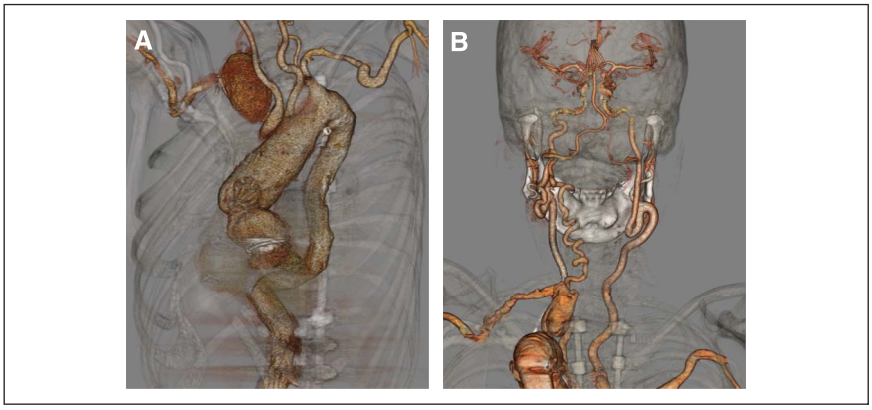
Loeys-Dietz syndrome (LDS) is a rare, autosomal dominant connective tissue disorder caused by variation in the genes that encode for the transforming growth factor (TGF)-β pathway, first described in 2005.[1] The mutated genes include *TGFBR1*, *TGFBR2*, *SMAD3*, *TGFB2*, *SMAD2*, and *TGFB3* and, along with related clinical features, are the basis for the classification of LDS into types 1 to 5, respectively.[2,3] Approximately 75% of cases are reported to arise because of de novo mutations.[4] The altered

Figure 1



Three-dimensional CT angiograms showing (**A**) 4.7 × 4.0-cm dilatation of the aortic root, 3.9-cm aneurysm of the ascending aorta, and 4.4 × 3.1-cm aneurysm of the right subclavian artery in an 18-year-old woman with Loeys-Dietz syndrome and (**B**) 5-mm aneurysm of the right internal carotid artery, occlusion of the right vertebral artery, and marked tortuosity of the internal carotid arteries in the same patient at age 25 years.

function of these genes results in an excess of TGF-β signaling and overproduction of the pathway's products, including connective tissue growth factor and collagen.[4] This aberrant molecular signaling can lead to a wide variety of phenotypic manifestations, with aortic and arterial aneurysms (Figure 1, A), dissections, and tortuosity (Figure 1, B) as key clinical features, sharing substantial clinical overlap with other connective tissue disorders, such as Marfan and Ehlers-Danlos syndromes.[2] Patients with LDS are additionally characterized by several distinctive physical features, including hypertelorism (Figure 2, A), cleft palate, bifid uvula (Figure 2, B), blue sclera, craniosynostosis, and arachnodactyly (Figure 2, C).[2-4]

Rapidly progressive aortic aneurysmal disease along with other vascular manifestations present the greatest immediate risks to patients with LDS because past investigations have reported aortic root dilatations in more than 95% of probands for LDS, aortic dissection as early as 6 months of age, and an average lifespan of 26 years for patients presenting with aneurysmal disease.[2,4-6] Given these comorbid presentations, cardiovascular disease is typically the focus of care and research associated with LDS.

However, a variety of musculoskeletal pathology has also been described in patients with LDS. These manifestations include idiopathic talipes equinovarus, scoliosis, spondylolisthesis, instability of the cervical spine, joint hypermobility, pectus deformity, osteoporosis, osteoarthritis, and deformity of the hip.[2,7-11] The reported orthopaedic conditions in LDS can vary considerably from patient to patient and can often be quite severe. Because early detection and improved management of the vascular aspects of the disease help patients with LDS live longer, fuller lives,[12] understanding these musculoskeletal manifestations will become increasingly important to optimize physical function and quality of life.

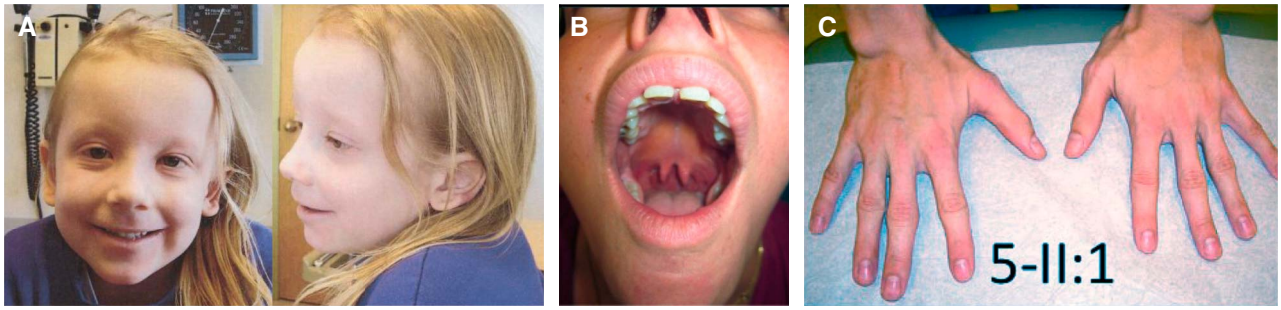
Although the musculoskeletal manifestations associated with LDS have previously been reported, the management of these conditions and associated outcomes have not been comprehensively described. Even among the general population, a broad spectrum of treatment approaches is available for many of the orthopaedic conditions reportedly associated with LDS, ranging from conservative measures, such as stretching and bracing treatment, to complex surgical procedures, such as multilevel spinal fusions. The severity of reported orthopaedic pathology coupled with the medical complexity of patients with LDS means that these challenging clinical decisions can be even more difficult to make for this population. Therefore, this systematic review aimed to provide a comprehensive evaluation of current literature regarding the management of orthopaedic conditions and associated outcomes in patients with LDS. It is our hope that this review will provide a valuable reference for pediatricians, orthopaedic surgeons, and anyone who provides care for patients with LDS.

Methods

Search Strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were used to review the databases of PubMed, Ovid MEDLINE, and Cochrane Library up to February 2020 using a reproducible search string (Supplemental Table 1, http://links.lww.com/JG9/A169).

Figure 2



Photographs demonstrating characteristic features of Loeys-Dietz syndrome: (**A**) hypertelorism, down-slanting palpebral fissures, amblyopia, and translucent skin in a 5-year-old girl, (**B**) bifid uvula in a 31-year-old woman, and (**C**) arachnodactyly in a 24-year-old man. (B and C) Adapted from Bertoli-Avella AM, Gillis E, Morisaki H, et al. Mutations in a TGF-β ligand, TGFB3, cause syndromic aortic aneurysms and dissections. *J Am Coll Cardiol* 2015;65 (13):1324-1336. Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

To be eligible for inclusion, articles must have reported primary data specifically regarding the management of orthopaedic conditions in patients with LDS. Exclusion criteria were review articles, conference abstracts, and articles without a full-text article published in English. Articles returned from each database through the selected search strings were compared, and duplicates were removed. Remaining articles were screened by title and abstract to include those that mentioned both LDS and an orthopaedic condition/procedure or the musculoskeletal system. Once irrelevant articles had been screened out, the full text of remaining articles was thoroughly reviewed for inclusion/exclusion criteria. A Preferred Reporting Items for Systematic Reviews and Meta-Analysis flow diagram detailing the full search strategy is shown in Figure 3.

Data Collection

Once the exclusion/inclusion criteria had been applied, data were extracted from each included article and organized using a MicroExcel spreadsheet. Data were collected from each study to describe the following variables: patients with a diagnosis of LDS, age at the last clinical follow-up, age at surgery, male and female patients, male and female patients undergoing orthopaedic surgery, numbers of patients with orthopaedic conditions documented, receiving conservative orthopaedic management undergoing orthopaedic surgery, requiring revision surgery, and experiencing adverse outcomes after surgery. Adverse outcomes were defined as any of the following during or after surgery: persistent, severe pain, markedly greater than expected blood loss, iatrogenic pathology, neurologic deficits, pseudarthrosis, instrumentation failure, revision surgeries, hemodynamic instability, and other perioperative medical complications. In addition, each included study was summarized for study design, key findings, indications, treatments, and outcomes (Supplemental Tables 2 and 3, http://links.lww.com/JG9/A169).

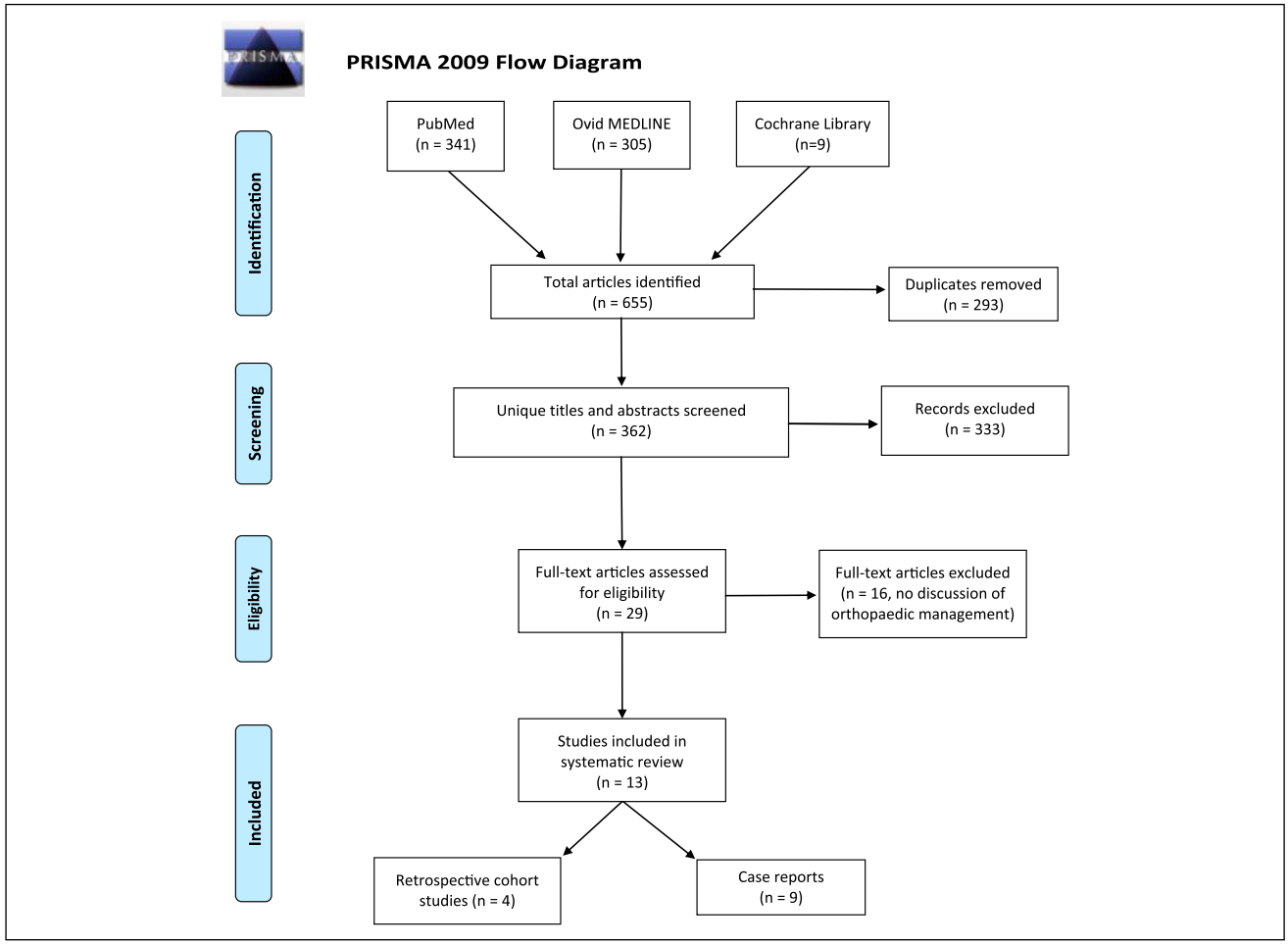
Data Analysis

The quality of included articles was assessed by two reviewers using the NIH study quality assessment tools for observational cohort and cross-sectional studies and for case series and the JBI critical appraisal checklist for case reports[22,23] (Table 1). For each included study, rates of the following were calculated as outcomes of interest: conservative management, surgical management, revision surgery, and adverse outcomes after surgical management. Rates of conservative management and surgical management were calculated by dividing the number of patients managed conservatively and managed surgically by the number of patients presenting with orthopaedic conditions. Rate of revision surgery was determined by dividing the number of patients requiring revision surgery by the number of patients managed surgically. Rate of adverse outcomes was determined by dividing the number of patients with adverse outcomes by the number of patients managed surgically.

Results

A total of 655 articles were returned, with 362 unique articles remaining after the duplicates were removed. After screening by title and abstract, 29 articles were identified for full-text review. Of these, 16 were excluded because they did not discuss the management of orthopaedic conditions. Finally, 13 articles were eligible for inclusion in this study, including four retrospective cohort studies[7,10,11,13] and nine case reports.[8,14-21]

Figure 3



Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram showing systematic literature search for orthopaedic management of Loeys-Dietz syndrome.

A total of 435 patients with LDS were described in the included studies. The mean reported patient age at the last clinical follow-up was 21.3 ± 16.1 years, and the mean age at the time of surgery was 9.0 ± 2.1 years. Approximately 49% of the included patients and 74% of those who underwent surgical intervention were female (Table 1).

In total, 120 cases of scoliosis, 82 cases of cervical deformity/instability, 37 cases of pectus excavatum, 26 cases of spondylolisthesis, and 11 cases of talipes equinovarus were described. Of the patients with LDS presenting with orthopaedic conditions, 10.3% received conservative (nonsurgical) management (among studies reporting conservative treatment) and 19.8% underwent surgical intervention. Of the 54 patients who received orthopaedic surgical care, 54.3% experienced one or more complications or adverse outcomes and 44.4% required subsequent revision surgery (Table 2).

Discussion

When LDS condition is discussed, devastating vascular pathology is often the focus of attention. With early identification, close surveillance, and aggressive management of vascular concerns, patients with LDS may be able to live longer, fuller lives, placing increased importance on effective management of the various orthopaedic conditions associated with LDS.[12,24] The literature regarding orthopaedic care for patients with LDS is relatively scarce. This study represents a comprehensive review of all currently available primary literature regarding treatment of orthopaedic conditions in this unique population.

Scoliosis

Connective tissue defects are largely at the root of the vascular complications associated with LDS but can also

Table 1. Study Demographics

Author	Study Type (Level of Evidence)	Quality Assessment	Patients With LDS (n)	Age at Final Follow-up (y) (mean ± SD)	Age at Surgery (y) (mean ± SD)	Female Patients in Cohort	Female Patients Undergoing Surgery
Kirby et al[13]	Retrospective cohort (IV)	8/11 (good)[a]	138	24 ± 17	7.7 ± —	50.7% (70)	—
Bressner et al[10]	Retrospective cohort (IV)	8/11 (good)[a]	141	—	12 ± 3	—	77.8% (7)
Fuhrhop et al[11]	Retrospective cohort (IV)	9/12 (good)[a]	80	17.3 ± 16.2	4 ± —	50.0% (40)	—
Erkula et al[7]	Retrospective cohort (IV)	7/10 (fair)[a]	65	21.4 ± 16.6	—	47.7% (31)	—
Heng et al[14]	Case report (V)		1	12	12	100% (1)	100% (1)
Rustagi et al[15]	Case report (V)	6/7[b]	1	11	11	0% (0)	0% (0)
Takebayashi et al[16]	Case report (V)	6/7[b]	1	20	20	0% (0)	0% (0)
Kuisle et al[17]	Case report (V)	8/8[b]	1	12	12	0% (0)	0% (0)
Kirmani et al[8]	Case report (V)	5/5[b]	2	21.5 ± 6.4	3 ± 2.8	0% (0)	0% (0)
Yakovlev et al[18]	Case report (V)	8/8[b]	1	31	4	0% (0)	0% (0)
Bunting and Bould[19]	Case report (V)	7/8[c]	1	12	12	0% (0)	0% (0)
Kamikado et al[20]	Case report (V)	8/8	1	11	11	0% (0)	0% (0)
Hadad et al[21]	Case series (IV)	7/8	2	18.5 ± 0.7	4.5 ± 4.9	50.0% (1)	50.0% (1)
Total			435	21.3 ± 16.1[d]	9.0 ± 2.1[d]	49.0%[d]	74.0%[d]

LDS = Loeys-Dietz syndrome
[a]NIH quality assessment for observational cohort and cross-sectional studies.[22]
[b]JBI critical appraisal for case reports.[23]
[c]NIH quality assessment for case series.[22]
[d]These totals based on incomplete data sets (not reported by all studies).

induce ligamentous laxity and defects in skeletal development, which lead to a wide variety of musculoskeletal comorbidities.[1,2] Among these various presentations, deformities of the spine seem to be the most commonly reported. Scoliosis was the most frequently reported condition among the studies we reviewed and has been observed among all five LDS subtypes.[3,7] However, scoliosis represents a broad spectrum of disease and individual cases that can range from relatively minor sagittal imbalances to severe spinal deformities, which can cause neurologic deficits and compromise respiratory function.[25,26] This broad range of severity is likely reflected among the patients with LDS we reviewed as well; of the 120 cases of scoliosis described, only 10% to 13% went on to require surgical management. Of the 88 patients with scoliosis in the cohort of Bressner et al[10] (62% of their included patients), 17% received nonsurgical treatment in the form of external bracing treatment. Mixed success was reported regarding this more conservative treatment with a mean curve progression of 12° ± 21° after bracing treatment and 47% of braced patients subsequently undergoing surgery. The reported rates of surgical intervention after bracing treatment of scoliotic patients in the general population vary substantially. A systematic review of adolescent idiopathic patients with scoliosis reported a surgical rate of 22% after bracing treatment[27]; however, a study of 88 patients with juvenile idiopathic scoliosis indicated a surgical rate of 50% for braced patients, which may be more in line with the result of Bressner et al.[28] Interestingly, Bressner

Table 2. Orthopaedic Treatment and Outcomes

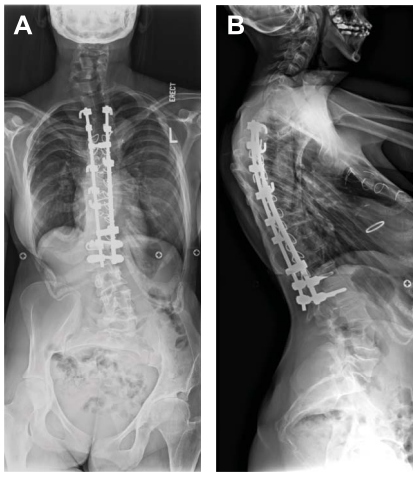
Author	Study Type	Condition Studied	Patients With Condition of Interest (n)	Treatment Received		Complications/ Adverse Outcomes	Revision Surgery
				Conservative	Surgical		
Kirby et al[13]	Retrospective cohort	Spondylolisthesis	23	—	47.8% (11)	45.5% (5)	36.4% (4)
Bressner et al[10]	Retrospective cohort	Scoliosis	88	17.0% (15)	10.2% (9)	—	55.6% (4)
Fuhrhop et al[11]	Retrospective cohort	Cervical deformity/ instability	61	8.2% (5)	14.8% (9)	77.8% (7)	77.8% (7)
Erkula et al[7]	Retrospective cohort	Cervical deformity/ instability	19	5.3% (1)	21.1% (4)	75.0% (3)	50.0% (2)
		Scoliosis	30	—	13.3% (4)	0% (0)	0% (0)
		Pectus excavatum	35	0% (0)	11.4% (4)	0% (0)	0% (0)
		Talipes equinovarus	11	—	27.3% (3)	100% (3)	33.3% (1)
		All	—	—			21.4% (3)
Heng[14]	Case report	Various	1	—	100% (1)	0% (0)	0% (0)
Rustagi et al[15]	Case report	Various	1	—	100% (1)	0% (0)	0% (0)
Takebayashi et al[16]	Case report	Cervical deformity/ instability	1	—	100% (1)	0% (0)	0% (0)
Kuisle et al[17]	Case report	Spondylolisthesis	1	—	100% (1)	100% (1)	0% (0)
Kirmani et al[8]	Case report	Various	2	—	100% (2)	50.0% (1)	50.0% (1)
Yakovlev et al[18]	Case report	Pectus excavatum	1	—	100% (1)	100% (1)	100% (1)
Bunting and Bould[19]	Case report	Fracture	1	—	100% (1)	100% (1)	100% (1)
Kamikado et al[20]	Case report	Scoliosis	1	—	100% (1)	100% (1)	100% (1)
Hadad et al[21]	Case series	Various	2	—	100% (2)	100% (2)	100% (2)
Total			278[a]	10.3%[b]	19.8% (54)	54.3%[b]	44.4% (24)

[a]These totals based on incomplete data sets (not reported by all studies).
[b]Totals from Erkula et al may include some overlap between conditions.

et al[10] reported no notable difference in curve progression based on whether braces were worn for greater or less than 18 hours per day. Furthermore, they reported no notable differences for age, sex, curve type, or magnitude between those who were successfully braced and those who subsequently required surgical intervention.

Although bracing treatment alone can be sufficient for some patients with scoliosis, surgery may be inevitable for others (Figure 4, A and B). The results are mixed regarding the outcomes of surgery for scoliosis in the population with LDS. Of the nine patients in the cohort of Bressner et al[10] who underwent surgery, six underwent posterior spinal fusion (PSF) and three received growing rod procedures. The clinically meaningful results were achieved for most patients after surgery with a mean curve correction of 73% reported for fusion

Figure 4



A, AP and (**B**) lateral radiographs of a 19-year-old woman with Loeys-Dietz syndrome who underwent T2-L2 anterior spinal fusion with posterior fixation at age 6 years.

procedures and 61% for growing rods in the cohort of Bressner et al.[10] However, spinal deformity procedures are known to be relatively morbid among the general population, with an 8.4% rate of serious adverse events reported in the National Surgical Quality Improvement Program database[29] and may be even more so for patients with LDS. Intraoperatively, Bressner et al[10] reported CSF leaks secondary to violation of the dura in almost a third of cases and total intraoperative blood loss >20% of the patient's total estimated blood volume in almost half. The authors suggested patients with LDS may be especially prone to such increased surgical morbidity because of vascular compromise secondary to abnormal connective tissue structure. Postoperatively, two of three patients who received growing rods experienced rod fractures, and five patients in total required revision surgery to extend fixation to additional levels of the spine. Of note, however, zero revision surgeries were reported among the four patients with scoliosis in the cohort of Erkula et al.[7] Given that their study was much broader in scope compared with Bressner's more specifically focused analysis, the relatively limited surgical information presented by Erkula et al makes it difficult to determine whether these surgical outcomes were due to differences in presentations/surgical technique or true differences across the population with LDS. The reported complication rates for surgical correction of scoliosis among the general population are substantially lower. A study of 6,334 adolescent patients with idiopathic scoliosis undergoing spinal fusion in the Scoliosis Research Society Morbidity and Mortality database reported a complication rate of 5.7% overall and 5.1% specifically for those who underwent posterior instrumentation and fusion.[30] Similarly, a smaller study of 546 patients from the Kids' Inpatient Database undergoing surgery for early onset scoliosis (age 0 to 10 years) reported an overall complication rate of 6%.[31]

Cervical Deformity/Instability

The next most prevalent orthopaedic condition among patients with LDS was cervical deformity or instability. Cervical instability has primarily been reported in association with LDS subtypes 1 and 2, although at least 1 case has been documented among both type 3 and type 5 patients.[3,7,11] Of the 82 reported cases, 15% to 21% of included patients underwent surgery and 5% to 8% trialed more conservative treatment. Fuhrhop et al[11] reported 61 total cases, with malformation of upper cervical vertebrae (C1-C3) in 76% and cervical instability in 16%. In contrast to the results of conservative management for scoliosis reported by Bressner et al, these authors reported that bracing treatment did prevent progression of deformity and/or neurologic deterioration among five patients with cervical deformity/instability. However, they noted that this conservative measure did not typically relieve symptoms or addressed radiologic deformity.[11] Therefore, although bracing treatment may reliably prevent conditions from worsening, more aggressive treatment may be required if patients are expected to markedly improve. Nine of the 61 patients with cervical deformity/instability in the cohort of Fuhrhop et al received surgical management, including 10 PSF, 2 anterior spinal fusions, and 1 case of halo traction. All patients who received surgical management had cervical instability preoperatively. Of the 10 PSF cases, 8 were limited to the cervical spine, whereas 2 spanned from the occiput to sacrum. Rates of revision surgery in this cohort were particularly high, with as many as 78% (7) requiring revision procedures. Adverse postoperative outcomes included five cases of pseudarthrosis, four cases of instrumentation failure, three cases of junctional kyphosis/instability, and 1 case of occipital-cervical instability. Erkula et al[7] reported similarly morbid outcomes among patients with cervical deformity/instability in their cohort, with 50% of patients requiring revision surgery and adverse outcomes in as many as 75%. Although reported outcomes for cervical pathology in patients with LDS are not encouraging, they must be carefully considered in the context of risk of potentially life-threatening spinal cord damage if cervical instability is left untreated.[32] Regarding the general population, a study including 914 patients with pediatric cervical fusion reported an overall postsurgical complication rate

of 26%.[33] A study of 11 patients with atlantoaxial instability undergoing cervical spinal fusion reported successful fusion in all patients but an overall complication rate of 64%.[34] Although only eight patients included in our review presented with atlantoaxial instability, overall complication rates for cervical fusion in patients with LDS may be more in line with figures reported for these procedures.

Spondylolisthesis

Defined as a sagittal malalignment or "slip" of a vertebral segment over the vertebrae immediately caudal, spondylolisthesis may be relatively common in the general population but can have serious consequences in more severe cases.[35] Although spondylolisthesis is often caused by osseous degeneration/deformation of the facet joints or fracture of the pars interarticularis, Kirby et al[13] hypothesized that in patients with LDS, spondylolisthesis may be more related to ligamentous laxity caused by connective tissue defects. Our review included 26 cases of spondylolisthesis, a substantial majority of which were among patients with LDS types 1 and 2; however, cases have been reported among those with types 3 to 5, although with less frequency.[3,7,13] Although this condition represents a lower proportion of the orthopaedic pathology described in our review, Kirby et al[13] highlighted the relative prevalence and severity of spondylolisthesis in patients with LDS. These authors reported a prevalence of 17% for spondylolisthesis in their cohort, which they noted to be substantially higher than the general population. The prevalence of spondylolisthesis has been estimated to be approximately 2% in children younger than 8 years[36] and 6.5% among athletes.[37]

Although Kirby et al[13] reported no notable difference in age at initial diagnosis between patients with low-grade versus high-grade spondylolisthesis, they did note that the degree of (preoperative) spondylolisthesis was markedly greater among patients who underwent surgery. Although spondylolisthesis in the general population is often mild enough to be managed conservatively,[35] 48% of patients with spondylolisthesis in the study by Kirby et al[13] received surgical treatment. All procedures among these 11 patients consisted of PSF, with or without posterior instrumentation. Overall, Kirby et al noted a notable reduction in vertebral slip, as assessed by Meyerding grade after surgical intervention. However, surgical intervention for spondylolisthesis may be associated with similar rates of adverse events as for other spinal conditions among patients with LDS. Kirby et al[13] reported that 45% of patients experienced adverse outcomes after surgery and 36% required revision surgery or additional procedures. Postoperative complications included pseudarthrosis, rod fracture, and severe, persistent pain. Again, the reported complication rate among patients with LDS is substantially higher than those documented for the surgical correction of spondylolisthesis among the general population. A study of 66,601 (primarily adult) patients in the National Inpatient Sample database undergoing posterior lumbar fusion for degenerative spondylolisthesis reported an overall complication rate of 13%,[38] and a study of spinal fusion for spondylolisthesis in pediatric patients reported an overall inpatient complication rate of 4.5% between 2003 and 2012.[39] Given the potential for spinal cord compression and cauda equina syndrome, spondylolisthesis may necessitate definitive surgical management in more severe cases.[40] However, physicians should be aware that although severe spondylolisthesis may be relatively common in patients with LDS, surgical intervention may be particularly risky for this population.

A single-patient report by Kuisle et al[17] described an interesting case of PSF for spondylolisthesis along with concomitant excision of an iliac osteochondroma in a 12-year-old boy with LDS. The procedure itself was largely successful; however, at 2 hours postoperatively, the patient experienced an acute hypotensive crisis. The patient was stabilized with appropriate medical management and determined to be suffering from primary adrenal insufficiency that was exacerbated by perioperative medications. The low overall prevalence and relatively recent initial characterization of LDS mean the full clinical picture of the syndrome has yet to be completely described and will continue to evolve. Therefore, it is unclear whether the complications of this case may be experienced by other patients with LDS. Perioperative hemodynamic instability is described in two additional case reports of orthopaedic surgery for patients with LDS. Bunting and Bould[19] reported a case of severe intraoperative hypotension that occurred during an arthroscopic repair of a tibial avulsion fracture and resolved 15 minutes after the procedure was halted and anesthesia was ceased. The authors surmised that this brief but severe episode of hypotension was likely related to the angiotensin receptor blocker the patient had been taking to mitigate risk of aortic dissection and report that the procedure was successfully done 3 days after this medication was discontinued. A case of transient, intraoperative hypotension was also reported by Kamikado et al[20] in an 11-year-old girl undergoing a T2-L4 surgical correction of severe scoliosis,

which prevented the completion of the rotational correction aspect of the procedure. Interestingly, this patient was not taking antihypertensive medications, and the authors suggested that this hemodynamic interruption was likely caused by compression of the right atria by the T9 vertebra during spinal rotation. Kamikado et al surmised that the arterial tortuosity characteristic of LDS may place the right atrium near the spine, putting these patients at an increased risk of right-sided cardiac compression. These reports of perioperative hemodynamic instability may present an important concern for the surgical management of patients with LDS and should be investigated further.

Pectus Excavatum

Disorders of the spine seem to be by far the most prevalent for the available orthopaedic literature for patients with LDS. However, a moderate number of patients LDS with other musculoskeletal manifestations have been reported as well. Pectus excavatum was reported among 36 patients with LDS between Erkula et al retrospective cohort and case reports by Yakovlev et al and Kirmani et al.[7,8,18] Pectus excavatum is a posterior depression of the sternum and surrounding cartilage interface which accounts for most congenital chest wall deformities.[41] Although this disorder can result in esthetic abnormalities, such as the appearance of a "sunken chest," more pressing concerns related to cardiopulmonary depression can necessitate surgical intervention.[41] Pectus deformities have been observed at relatively high rates among patients with all five types of LDS.[3,7] Only 11% of patients with LDS with pectus excavatum in the cohort of Erkula et al[7] required surgical intervention,[7] and no notable complications, adverse outcomes, or revision surgeries were reported. Demonstrating the variability among patients with LDS, however, a case report by Yakovlev et al[18] described a much more complicated clinical course. This patient initially underwent a pectus deformity repair at the age of 4 years and went on to require two revision procedures at ages 10 and 21 years, including removal of previously placed implant.

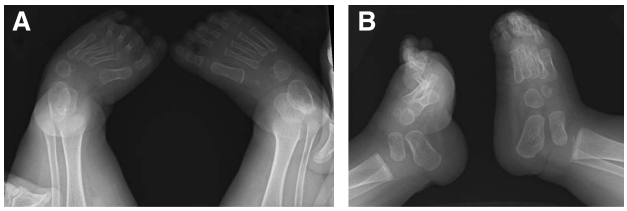
Other Musculoskeletal Conditions

Talipes equinovarus, or clubfoot deformity (Figure 5, A and B), was reported among 11 patients with LDS in Erkula et al[7] mixed cohort of orthopaedic patients. Their analysis indicated that although most of these 11 were treated with serial casting, three underwent surgical correction in the form of a subtalar soft-tissue release. All three of these patients subsequently demonstrated hindfoot valgus or metatarsus adductus after surgery and although one required a calcaneal osteotomy for the correction of hindfoot deformity, none of the three reported lasting postoperative pain.

In addition to the more frequently published diagnoses reported among retrospective cohorts, several other musculoskeletal conditions were included among reports of patients with LDS, such as hip deformity[7,15] and lower extremity fractures.[8,14,19] The risk of fractures in patients with LDS has been documented and may often be associated with decreased bone density, possibly related to mutations in TGF-β pathways.[9,42] However, surgical management of these fragility fractures has not been well described. Similarly, an assortment of hip pathology has been reported in patients with LDS, including osteonecrosis, arthritis, and acetabular protrusion[7,15] (Figure 6, A and B). A limited number of cases have been described, but no evidence currently exists to suggest that these conditions should be managed differently or more aggressively in LDS compared with the general population. As such, asymptomatic patients can likely be managed conservatively, and a standard progression of care can be followed for those who are symptomatic.

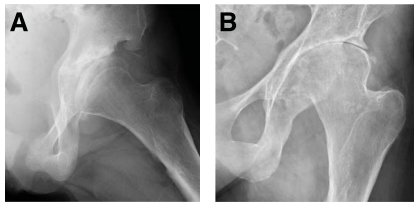
Many of the musculoskeletal manifestations described in patients with LDS, such as spinal deformity, osteoarthritis, and hip dysplasia, along with increased rates of complications, have also been associated with other connective tissue disorders, such as Marfan and Ehlers-Danlos syndromes. Future clinical studies will be

Figure 5



A, AP and (**B**) lateral radiographs demonstrating clubfoot deformity in a 10-month-old girl with Loeys-Dietz syndrome.

Figure 6



AP radiographs of the left hip in a female patient with Loeys-Dietz syndrome (**A**) at age 12 years showing flattening of the femoral head and shallow acetabulum and (**B**) at age 25 years showing chronic bony remodeling and severe osteoarthritis of the hip joint.

important to understand how orthopaedic outcomes may coincide or differ among such patients and to what extent previous data from patients with other connective tissue disorders may inform care and prognosis for patients with LDS.[43-45]

Limitations

This study represents the first comprehensive literature review of the management of musculoskeletal manifestations of LDS and the outcomes of these various interventions. However, this systematic review is not without limitations. First, the heterogeneity of diagnoses and limited quantitative data reported by some included studies limited our ability to provide complete statistical analysis of management and outcomes. In particular, outcomes for patients with LDS were not directly compared with patients with non-LDS with similar orthopaedic conditions and all included studies presented level IV or V evidence. In addition, our inclusion of multiple case reports may bias our analysis toward higher complication rates because complications were the main reason a report had been published in some cases. All four of the included cohort studies, which make up the bulk of reported cases, were produced by authors at The Johns Hopkins University,[7,10,11,13] where the molecular basis and formal diagnosis of LDS were initially identified and described. This may have led to multiple descriptions of the same patients between studies, and referencing this single-institution cohort may limit generalizability to the general population. Furthermore, a preponderance of the included cases and studies focused on spinal pathology associated with LDS. Although spinal deformity and instability is clearly of great concern for this population, additional exploration of lesser-reported conditions, such as pathological fractures, hip deformity, and talipes equinovarus, is warranted. Therefore, additional studies should be done to characterize orthopaedic diagnosis and management among patients with LDS in a broader array of regional and institutional settings with a specific focus on stratification by orthopaedic diagnosis.

Conclusion

Overall, orthopaedic conditions seem to be relatively common among patients with LDS. Although disorders of the spine are most commonly reported, a host of other pathologies of both the axial and appendicular musculoskeletal system has been described. Trials of conservative management were reported for approximately 1 in 10 of these patients, with varying levels of success. For some, treatments, such as bracing treatment, were sufficient, whereas others went on to require more definitive surgical intervention. Just below one in five of the patients presenting with orthopaedic pathology underwent surgical management of some kind. The patients who did receive these more invasive treatments tended to be relatively young; the average age at surgery was 9.1 ± 2 years. For patients who did undergo surgery, surgical outcomes were quite morbid. Approximately half experienced at least one adverse outcome and slightly fewer required revision surgery or revision. In summary, this is a population with a relatively high prevalence of severe orthopaedic pathology presenting in childhood or early adolescence that is at substantial risk of surgical complications. Given the complex nature of this disorder and the limitations of literature on the topic, additional high-quality research is imperative.

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References

1. Loeys BL, Chen J, Neptune ER, et al: A syndrome of altered cardiovascular, craniofacial, neurocognitive and skeletal development caused by mutations in TGFBR1 or TGFBR2. *Nat Genet* 2005;37:275-281.

2. MacCarrick G, Black JH III, Bowdin S, et al: Loeys-Dietz syndrome: A primer for diagnosis and management. *Genet Med* 2014;16:576-587.

3. Schepers D, Tortora G, Morisaki H, et al: A mutation update on the LDS-associated genes TGFB2/3 and SMAD2/3. *Hum Mutat* 2018;39: 621-634.

4. Loeys BL, Dietz HC: Loeys-Dietz syndrome, in Adam MP, Ardinger HH, Pagon RA, et al, eds: *GeneReviews*. Seattle, WA, University of Washington, 2008.

5. Loeys BL, Schwarze U, Holm T, et al: Aneurysm syndromes caused by mutations in the TGF-beta receptor. *N Engl J Med* 2006;355:788-798.

6. Loughborough WW, Minhas KS, Rodrigues JCL, et al: Cardiovascular manifestations and complications of Loeys-Dietz syndrome: CT and MR imaging findings. *Radiographics* 2018;38:275-286.

7. Erkula G, Sponseller PD, Paulsen LC, Oswald GL, Loeys BL, Dietz HC: Musculoskeletal findings of Loeys-Dietz syndrome. *J Bone Joint Surg Am* 2010;92:1876-1883.

8. Kirmani S, Tebben PJ, Lteif AN, et al: Germline TGF-beta receptor mutations and skeletal fragility: A report on two patients with Loeys-Dietz syndrome. *Am J Med Genet A* 2010;152A:1016-1019.

9. Tan EW, Offoha RU, Oswald GL, et al: Increased fracture risk and low bone mineral density in patients with Loeys-Dietz syndrome. *Am J Med Genet A* 2013;161A:1910-1914.

10. Bressner JA, MacCarrick GL, Dietz HC, Sponseller PD: Management of scoliosis in patients with Loeys-Dietz syndrome. *J Pediatr Orthop* 2017;37:e492-e499.

11. Fuhrhop SK, McElroy MJ, Dietz HC III, MacCarrick GL, Sponseller PD: High prevalence of cervical deformity and instability requires surveillance in Loeys-Dietz syndrome. *J Bone Joint Surg Am* 2015;97:411-419.

12. Aftab M, Cikach FS, Zhu Y, et al: Loeys-Dietz syndrome: Intermediate-term outcomes of medically and surgically managed patients. *J Thorac Cardiovasc Surg* 2019;157:439-450.e5.

13. Kirby DJ, Dietz HC, Sponseller PD: Spondylolisthesis is common, early, and severe in Loeys-Dietz syndrome. *J Pediatr Orthop* 2018;38: e455-e461.

14. Heng C: Stress fractures in Loeys-Dietz syndrome. *Int Arch Orthop Surg* 2019;2. doi:10.23937/2643-4016/1710008.

15. Rustagi T, Agashe MV, Dhamele J, Aroojis AJ, Mehta R: Loeys-Dietz syndrome with bilateral radial head dislocations: A case report. *J Orthop Surg* 2013;21:262-265.

16. Takebayashi K, Kubota M, Yuzurihara M, Tachibana S, Kawamata T: The transspinal canal screwing technique for atlantoaxial anomalies: A technical note and 2 case reports. *Neurospine* 2019;16:293-297.

17. Kuisle AM, Gauguet S, Karlin LI, Dauber A, McCann ME: Postoperative adrenal crisis in an adolescent with Loeys-Dietz syndrome and undiagnosed adrenoleukodystrophy. *Can J Anaesth* 2011;58:392-395.

18. Yakovlev AE, Resch BE, Karasev SA: Treatment of chronic chest wall pain in a patient with Loeys-Dietz syndrome using spinal cord stimulation. *Neuromodulation* 2011;14:27-29.

19. Bunting AC, Bould MD: Hemodynamic instability during anesthesia in an adolescent with Loeys-Dietz syndrome: A case report. *Paediatr Anaesth* 2014;24:1302-1304.

20. Kamikado Y, Mihara T, Ka K: Anesthetic management of a pediatric patient with Loeys-Dietz syndrome: A case report. *Paediatr Anaesth* 2019;29:875-877.

21. Hadad MJ, Abousamra O, Sullivan BT, Sponseller PD: Occiput-to-pelvis spinal arthrodesis: A case Series. *Spine Deform* 2019;7:992-1002.

22. Study quality assessment tools. https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools. Accessed July 28, 2021.

23. Critical appraisal tools. https://jbi.global/critical-appraisal-tools. Accessed July 28, 2021.

24. Patel ND, Crawford T, Magruder JT, et al: Cardiovascular operations for Loeys-Dietz syndrome: Intermediate-term results. *J Thorac Cardiovasc Surg* 2017;153:406-412.

25. Blevins K, Battenberg A, Beck A: Management of scoliosis. *Adv Pediatr* 2018;65:249-266.

26. Altaf F, Gibson A, Dannawi Z, Noordeen H: Adolescent idiopathic scoliosis. *BMJ* 2013;346:f2508.

27. Dolan LA, Weinstein SL: Surgical rates after observation and bracing for adolescent idiopathic scoliosis: An evidence-based review. *Spine* 2007; 32(19 suppl):S91-S100.

28. Khoshbin A, Caspi L, Law PW, et al: Outcomes of bracing in juvenile idiopathic scoliosis until skeletal maturity or surgery. *Spine* 2015;40:50-55.

29. Pugely AJ, Martin CT, Gao Y, Ilgenfritz R, Weinstein SL: The incidence and risk factors for short-term morbidity and mortality in pediatric deformity spinal surgery: An analysis of the NSQIP pediatric database. *Spine* 2014; 39:1225-1234.

30. Coe JD, Arlet V, Donaldson W, et al: Complications in spinal fusion for adolescent idiopathic scoliosis in the new millennium. A report of the Scoliosis Research Society Morbidity and Mortality Committee. *Spine* 2006;31:345-349.

31. Rustagi T, Kurra S, Sullivan K, Dhawan R, Lavelle WF: Surgical treatment of early-onset idiopathic scoliosis in the United States: A trend analysis of 15 years (1997-2012). *Spine J* 2019;19:314-320.

32. Rahimi SY, Stevens EA, Yeh DJ, Flannery AM, Choudhri HF, Lee MR: Treatment of atlantoaxial instability in pediatric patients. *Neurosurg Focus* 2003;15:ECP1.

33. Hwang SW, Gressot LV, Rangel-Castilla L, et al: Outcomes of instrumented fusion in the pediatric cervical spine. *J Neurosurg Spine* 2012;17:397-409.

34. Tauchi R, Imagama S, Ito Z, et al: Complications and outcomes of posterior fusion in children with atlantoaxial instability. *Eur Spine J* 2012;21: 1346-1352.

35. Randall RM, Silverstein M, Goodwin R: Review of pediatric spondylolysis and spondylolisthesis. *Sports Med Arthrosc* 2016;24:184-187.

36. Lemoine T, Fournier J, Odent T, et al: The prevalence of lumbar spondylolysis in young children: A retrospective analysis using CT. *Eur Spine J* 2018;27:1067-1072.

37. Rossi F, Dragoni S: The prevalence of spondylolysis and spondylolisthesis in symptomatic elite athletes: Radiographic findings. *Radiography* 2001;7:37-42.

38. Kalanithi PS, Patil CG, Boakye M: National complication rates and disposition after posterior lumbar fusion for acquired spondylolisthesis. *Spine* 2009;34:1963-1969.

39. Rumalla K, Yarbrough CK, Pugely AJ, Dorward IG: Spinal fusion for pediatric spondylolisthesis: National trends, complications, and short-term outcomes. *Neurosurgery* 2018;82:701-709.

40. Alfieri A, Gazzeri R, Prell J, Röllinghoff M: The current management of lumbar spondylolisthesis. *J Neurosurg Sci* 2013;57:103-113.

41. Jaroszewski D, Notrica D, McMahon L, Steidley DE, Deschamps C: Current management of pectus excavatum: A review and update of therapy and treatment recommendations. *J Am Board Fam Med* 2010;23: 230-239.

42. Ben Amor IM, Edouard T, Glorieux FH, et al: Low bone mass and high material bone density in two patients with Loeys-Dietz syndrome caused by transforming growth factor beta receptor 2 mutations. *J Bone Miner Res* 2012;27:713-718.

43. Al Kaissi A, Zwettler E, Ganger R, Schreiner S, Klaushofer K, Grill F: Musculo-skeletal abnormalities in patients with Marfan syndrome. *Clin Med Insights Arthritis Musculoskelet Disord* 2013;6:1-9.

44. Stanitski DF, Nadjarian R, Stanitski CL, Bawle E, Tsipouras P: Orthopaedic manifestations of Ehlers-Danlos syndrome. *Clin Orthop Relat Res* 2000:213-221.

45. Chung AS, Renfree S, Lockwood DB, Karlen J, Belthur M: Syndromic scoliosis: National trends in surgical management and inpatient hospital outcomes: A 12-year analysis. *Spine* 2019;44: 1564-1570.