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Predictors of low bone density and fracture risk in Loeys–Dietz syndrome

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Abstract

Purpose: Loeys–Dietz syndrome (LDS) is a connective tissue disorder affecting multiple organ systems, including bone.

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Ethics Declaration

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the National Institutes of Health's institutional review board. Informed consent was obtained from all participants. Patients/guardians have consented to publication in writing.

Additional Information

The online version of this article (https://doi.org/10.1016/j.gim.2021.10.002) contains supplementary material, which is available to authorized users.

Conflict of Interest

The authors declare no conflict of interests.

Methods: We defined the bone phenotype and clinical predictors of low bone density and fracture risk in 77 patients with LDS type 1 to type 5.

Results: Patients with LDS had dual-energy x-ray absorptiometry (DXA) Z-scores significantly < 0, and 50% of children and 9% of adults had Z-scores < −2. Sixty percent of patients had ≥1 fracture, and 24% of patients with spinal x-rays scans showed spinal compression fractures. Lower body mass index, asthma, male sex and eosinophilic gastrointestinal disease were correlated with lower DXA Z-scores. The count of 5 LDS-associated skeletal features (scoliosis, pes planus, arachnodactyly, spondylolisthesis, and camptodactyly) in patients with LDS was correlated with DXA Z-score. Adults with ≥1 skeletal features had DXA Z-scores significantly < 0, and children with >2 features had DXA Z-score significantly < −2. Bone turnover markers suggest accelerated bone resorption. Data from 5 patients treated with bisphosphonates suggest a beneficial effect.

Conclusion: All LDS types are associated with reduced bone density and increased risk of fracture, which may be due to increased bone resorption. Clinical features can predict a subgroup of patients at highest risk of low bone density and fracture risk.

Keywords

Bone density; DXA; Fracture risk; TGFβ

Introduction

Loeys–Dietz syndrome (LDS) is an autosomal-dominant connective-tissue disorder initially characterized by aortic aneurysms and generalized arterial tortuosity, hypertelorism, and bifid uvula/cleft palate resulting from pathogenic variants in genes in the TGFβ pathway. LDS types 1 (OMIM 609192) and 2 (OMIM 610168) were the first ones to be described, which were caused by pathogenic variants in *TGFBR1* (OMIM 190181) or *TGFBR2* (OMIM 190182) encoding TGFβ receptor subunits 1 and 2, respectively.[1,2] The phenotype of patients with type 1 and 2 LDS was recently found to include a predisposition to develop nearly all forms of allergic disease as well as inflammatory bowel disease.[3,4] LDS has now expanded to include types 3 (OMIM 613795), 4 (OMIM 614816), and 5 (OMIM 615582) resulting from pathogenic variants in *SMAD3* (OMIM 603109),[5,6] *TGFB2* (OMIM 190220),[7] and *TGFB3* (OMIM 190230),[8] respectively. The skeletal phenotype of all forms of LDS includes joint laxity, arachnodactyly, camptodactyly, malar hypoplasia, high arched/cleft palate, pes planus, pectus deformity, scoliosis, cervical spine abnormalities (vertebral malformations/hypoplasia, subluxation, malalignment/instability,[9] and spondylolisthesis).[1,2,10-13] Additional studies limited to LDS types 1 and 2 have suggested that skeletal fragility and low bone mineral density may also be features of LDS, but it is not clear whether this relates to their primary genetic defect or associated immunologic comorbidities or whether this association is present in all forms of LDS. With advancements in the cardiovascular care of patients with LDS, issues such as osteopenia and fracture risk become increasingly relevant.

There is a wide phenotypic spectrum of disease severity in LDS even within the same type. We therefore undertook to better define the bone phenotype in the different types of LDS; define predictive models that can identify those at risk for skeletal morbidity, defined

as low bone density and fracture risk; and investigate whether defects in bone resorption or formation contribute to the skeletal phenotype, which may have important therapeutic implications.

Materials and Methods

Study participants

Participants with a pathogenic variant in *TGFBR1, TGFBR2, SMAD3, TGFB2*, or *TGFB3* and a diagnosis of LDS were enrolled in a natural history study at the National Institutes of Health. First degree relatives were included in the study only if they had a genetically confirmed diagnosis of LDS. All participants had clinical findings associated with LDS. Patients underwent clinical evaluation, including history and physical examination, dual-energy x-ray absorptiometry (DXA) scan, and blood work (including measurement of markers of bone metabolism [Supplemental Table 1], including bone turnover markers procollagen 1 intact N-terminal propeptide [P1NP] and C-terminal telopeptide of type 1 collagen [CTX], drawn in the morning). DXA Z-scores for patients aged <18 years were adjusted for height and age as.[14] For analysis of whole-body DXA Z-score, the adjusted whole-body DXA Z-score (whole body minus head) was used for patients aged <18 years, whereas whole-body DXA Z-score was used for patients aged ≥18 years.[15] Skeletal features of LDS used in the predictive models were assessed by a team of clinicians with expertise in LDS and confirmed by a review of the patients' medical records.

Statistical analysis

Wilcoxon signed-rank tests were performed to compare the DXA Z-scores to 0 and Wilcoxon rank sum tests to compare the DXA Z-scores between groups of subjects (children vs adults; LDS types 1/2 vs types 3/4/5). Linear regression models predicting DXA Z-scores and multivariate data analysis were performed as discussed in the Supplemental Methods. The primary goal of this work is descriptive, and because these analyses were exploratory, no adjustment was made for multiplicity; consequently *P*-values should be interpreted cautiously.

Results

Characteristics of study participants

A total of 77 patients with a confirmed genetic diagnosis of LDS were enrolled, including 33 adults (aged ≥18 years) and 44 children. Demographic, laboratory, and skeletal feature characteristics are summarized in Table 1. Genotype data is listed in Supplemental Table 2. Most patients were diagnosed with LDS types 1 and 2 ($n = 22$ and $n = 33$, respectively) with the remaining 22 being diagnosed with types 3 ($n = 10$), 4 ($n = 9$), and 5 ($n = 3$). Forty percent were male. The patients were aged 2 to 68 years with a mean age of 22 years. Patients had on average approximately 3 skeletal features characteristic of LDS with most patients having pes planus, pectus deformity, and scoliosis. Nearly half had arachodactyly, about 20% had cervical spine abnormalities and campodactyly, and about 5% had spondylolisthesis.

Patients with LDS exhibit skeletal fragility and increased risk of fractures that is modified by age, sex, body mass index, and LDS type

Median DXA Z-scores at all sites (whole body, spine, hip, and forearm) were significantly < 0 ($P < .0001$ for all) for patients with LDS as a group. However, some differences were seen based on age. When adults and children were analyzed as subgroups, it was observed that whereas DXA Z-scores for only the spine and hip were significantly < 0 in adults, those of all sites were less significantly < 0 in children ($P < .0001$ for children for whole body, spine, hip, and forearm and $P = .0017$ for adult spine and $P = .0002$ for adult hip) (Figure 1A and B, Supplemental Figure 1). Through whole-body DXA, it was seen that 9.1% of adults and 50% of children had low bone density with Z-scores < −2. There was no difference in DXA Z-scores at any site on the basis of the type of LDS in either children or adults. Patients with type 5 LDS appeared to have higher Z-scores at some sites, but sample size was very limited (2 adults and 1 child) and the differences were not statistically significant overall when comparing differences across types.

Sixty percent of patients experienced ≥1 lifetime fracture. The median number of lifetime fractures was 1 (range = 0-6). Fractures were most common in children with types 1 and 2 LDS but were more evenly distributed across LDS types in adults (Figure 1C). A total of 82 fractures were confirmed by x-ray in our cohort, 42 in children and 40 in adults. Of them, 20% were reported to occur after minimal trauma. Lateral spine films were used to screen for vertebral compression fractures in 17 children on the basis of clinical concern (back pain and/or low lumbar spine bone density); of these, 4 (24%) showed spinal compression fractures. A fifth patient had a spinal fracture secondary to trauma. A list of specific fracture sites is listed in Supplemental Table 3.

Body mass index (BMI) percentile was highly associated with whole body, spine, hip, and forearm DXA Z-scores after adjusting for binary age (child vs adult; Supplemental Figure 2). Overall, patients who had lower BMIs exhibited a greater propensity for low bone density.

Males had a significantly lower spine DXA Z-score than females after adjusting for binary age ($P = .041$). No difference between sexes reached significance in DXA Z-score results for whole body, hip, or forearm (Supplemental Figure 3).

Greater number of skeletal features is associated with poor bone health in LDS

Skeletal abnormalities are commonly present in LDS, including scoliosis, pectus deformity, pes planus, arachnodactyly, spondylolisthesis, cervical spine abnormalities, and camptodactyly. We initially observed that the simple count of these 7 skeletal defects correlated very highly with DXA Z-scores; this observation was further refined with several multivariate analyses that indicated that cervical spine abnormalities and pectus deformity do not appear to add to the predictive ability of the skeletal count endpoint (see Supplemental Material for details). We therefore scored patients on how many of these 5 skeletal defects common in LDS they manifested. Of these 5 features, children had a mean of 2.2 total skeletal features, whereas adults had a mean of 2. For both adults and children, the Z-score for the whole-body DXA was inversely correlated with the total number of

skeletal features. (Figure 2A; for adults, Spearman's r = −0.596, $P < .001$; for children, Spearman's r = −0.657, $P < .0001$). See Supplemental Figure 4 for spine, hip, and forearm DXA vs the number of skeletal features. For children, the number of fractures per year of life also correlated with the number of skeletal abnormalities (Figure 2B; Spearman's r = 0.409, $P = .006$).

In a regression model using binary age and the 5 individual skeletal features used in the skeletal count to predict whole-body DXA Z-scores, only scoliosis and arachnodactyly were identified as independent statistically significant predictors. The importance of these 2 features was further supported by a stepwise variable selection starting with binary age and the 5 individual skeletal features in the skeletal count that also selected these 2 features. Although the count of all 5 features as a single variable was more predictive than these 2 features, these analyses provide some evidence that scoliosis and arachnodactyly may best reflect the skeletal phenotype that results in low DXA Z-score and increased fracture risk.

Decision trees can predict risk for skeletal morbidity in LDS

Given the wide variability in DXA Z-scores, we sought to develop a scoring system that could be used by clinicians to determine which patients with LDS are at highest risk for skeletal morbidity. In this analysis, the following clinical and laboratory variables were considered in the model as predictors of whole-body DXA Z-score: BMI, height, weight, parathyroid hormone, 25-hydroxy vitamin D, P1NP, CTX, sex, individual allergic or inflammatory features (asthma, eczema, allergic rhinitis, food allergy, milk avoider, any eosinophilic gastrointestinal [GI] disease), any allergic or inflammatory feature, any inflammatory GI disease, scoliosis, pectus deformity, pes planus, arachnodactyly, spondylolisthesis, cervical spine abnormalities, camptodactyly, the number of skeletal features (out of 5), binary age (adult vs child), binary LDS type (type 1/2 vs type 3/4/5), continuous age, and LDS type (5 groups). Of these features, only 2 were significant in predicting whole-body DXA Z-score: count of skeletal features and binary age (adult vs child). First, dividing subjects into categories on the basis of the number of skeletal features (≤1 or >1) was highly significantly associated with whole-body DXA Z-scores ($P < .001$), with subjects exhibiting none or 1 feature having higher scores than those with >1 feature. Among the subjects who had at least 1 skeletal feature, age provided additional predictive information. In the subset who had at least 1 skeletal finding, dividing the subjects on the basis of binary age (children vs adults) was significantly associated with whole-body DXA Z-score ($P < .001$). Of the children with >1 skeletal feature, dividing again on the basis of having a skeletal count of 2 vs a skeletal count of > 2 was significantly associated with whole body DXA Z-score ($P = .013$). The decision tree is illustrated in Figure 3.

Subjects, regardless of age, with 0 or 1 skeletal feature had whole-body DXA Z-scores that were normal and not significantly different than 0 ($P = .78$). Adults with >1 skeletal feature had DXA Z-scores that were significantly < 0 ($P = .008$). Children with LDS with >1 skeletal feature had whole-body DXA Z-scores that were significantly < 0 regardless of the total number of skeletal features they exhibited; however, those with >2 skeletal features had a DXA Z-score that was significantly lower than those with 2 features ($P = .038$). In

addition, the whole-body DXA Z-score was significantly < −2 SD below normal (median = −2.76, $P < .01$) in those children with 2 or more skeletal features.

A similar decision tree analysis was also undertaken to identify predictors of fractures per year of life. In this analysis, a diagnosis of asthma was the only significant variable ($P = .001$) identified that predicted risk, with subjects having a history of asthma exhibiting significantly more fracture per year of life than subjects without asthma (median = 0.08 fractures per year of life vs 0 fractures per year of life). Asthma was also significant ($P = .002$) in the univariate analysis to predict fractures per year of life, after adjusting for binary age.

The role of allergic disease in skeletal morbidity in LDS

Previous studies have suggested that allergic disease and gastrointestinal inflammation can adversely affect bone health. We therefore assessed whether diagnoses of allergic rhinitis, any eosinophilic GI disease (EGID), any inflammatory GI disease, asthma, asthma/eczema/allergic rhinitis, eczema, eosinophilic colitis, eosinophilic esophagitis, eosinophilic gastroenteritis, food allergy, and any allergic/inflammatory feature were predictive of bone density where each predictor was evaluated in its own model, adjusting for binary age. Although there appear to be some differences in whole-body DXA Z-score between subjects with and without these features, they are not significant after adjusting for binary age. This illustrates the importance of taking age into account because children are more likely to have allergic disease because what might first appear to be an association with allergic disease may be due to confounding with age. To evaluate the contribution of allergic disease more comprehensively in a fully multivariate context, we used a stepwise selection model approach. The results of this model to predict whole-body DXA Z-score are presented in Supplemental Table 4. Having any EGID is significantly associated with a lower whole-body DXA Z-score of −0.77 on average. Other variables selected by this stepwise algorithm are BMI ($\beta_1 = 0.09$), skeletal count ($\beta_1 = -0.77$), and eczema ($\beta_1 = -0.46$), with lower BMI and a greater number of skeletal features significantly predicting worse bone density. Given the preponderance of allergic disease in LDS types 1 and 2 as well as most low DXA Z-scores being in patients with these LDS types, it is possible that models considering allergic disease would simply be selecting conditions present in LDS types 1 and 2. However, when limiting the subjects to only those with LDS types 1 and 2, the same model is selected (Supplemental Table 5), suggesting that the association across all types is reflective of a true association.

Bone turnover markers suggest increased bone resorption in LDS

To investigate the mechanism underlying bone fragility in LDS, laboratory measurements of P1NP and CTX were performed, and age-related Z-scores were calculated. P1NP is a marker of bone formation, which is created when the amino terminus of the procollagen trimer is cleaved as part of the formation of tropocollagen. CTX is a marker of bone resorption or breakdown and is a fragment of the alpha-1 peptide released when the osteoclast processes the bone collagen. The levels of these proteins are significantly affected by the linear growth velocity, and normative values are currently not available for children; thus, children were excluded from these analyses. The Z-score of CTX was inversely correlated to Z-score of the whole-body bone density, suggesting increased bone resorption

in LDS (Spearman's r = −0.47, $P = .017$; Supplemental Figure 5). There was no correlation between P1NP and DXA Z-score (Supplemental Figure 6).

Case studies suggest utility of bisphosphonates in treating low bone density in patients with LDS

Five pediatric patients (3 girls and 2 boys) had a history of bisphosphonate treatment, which was initiated on clinical grounds on the basis of low bone density and a clinically significant fracture history. Patient characteristics are noted in Supplemental Table 3. The median age at bisphosphonate initiation was 14 years (range = 11–17 years), and the median treatment duration was 1 year (range = 4 months-5.5 years). Formulations varied between patients, including zoledronate ($n = 3$), a combination of pamidronate and zoledronate ($n = 1$), and alendronate ($n = 1$). Of these patients, 3 had type 1 LDS and 2 patients had type 2 LDS.

Patient DXA Z-scores over time are shown in Figure 4. All patients exhibited improvement in their DXA Z-score in the forearm and femoral neck after initiation of treatment, whereas 4 of 5 had increased Z-score relative to baseline in the total hip. Response in the whole body and spine were less consistent, with improvement in only 2 of 4 and 1 of 3 patients. However, data at these sites was limited because of the presence of spinal hardware.

Discussion

LDS is an autosomal-dominant connective tissue disorder with involvement of multiple organ systems, including bone. The genetic cause of LDS is heterogeneous, with pathogenic variants in several genes in the TGFβ signaling pathway identified, including *TGFBR1, TGFBR2, SMAD3, TGFB2*, and *TGFB3*, leading to LDS type 1, type 2, type 3, type 4, and type 5, respectively. In this study, we examined bone health in the largest cohort of patients with LDS to date, including those with types 3, 4, and 5 LDS, and identified clinical and laboratory parameters that can predict skeletal morbidity and potentially guide treatment in this population.

TGFβ proteins are a family of cytokines present in large amounts in bone and cartilage that modulate the activity of osteoblasts and osteoclasts, and couple bone resorption and formation.[16-18] TGFβ has been shown to regulate the mechanical properties and composition of bone matrix,[19] and disruption of the TGFβ signaling pathway results in bone abnormalities, including hyperostosis in patients with Camurati–Engelmann disease who exhibit excessive TGFβ signaling,[20,21] and low bone density and a predilection for fractures in LDS. A previous survey-based study of 57 respondents with LDS types 1 and 2 found 3.9 fractures per 100 person-years (compared with 2.3-2.4 fractures per 100 person-years in the general population[22]) and a 50% risk of fracture by age 14 years. In that study, 17 of the survey respondents had DXA scans performed for clinical indications, and of those, about 60% exhibited a DXA Z-score > 1 SD below normal in the spine, hip, and/or femoral neck;[9] whole body DXA Z-scores were not evaluated in this study. In our study, we performed DXA scans in 77 consecutive patients with LDS types 1 to 5 and found that one-third of adults and 59% of children with LDS exhibited poor bone health (whole body DXA Z-score ≥ 1 SD below normal), with no significant differences in DXA Z-scores across different types of LDS. Children, but not adults, with LDS types 1 and 2 had significantly more

fractures per year of life than those with types 3, 4, or 5 ($P = .02$). Overall, 61% of the 77 patients with LDS in our cohort experienced at least 1 fracture in their lifetime. Overall, children exhibited worse bone health than adults with LDS. There are at least 2 possible explanations for this observation. One is that the phenotype improves with age. The other is that there is a survival and/or referral bias for more severely affected children. We strongly suspect the latter explanation is more likely; however, a longitudinal study would be required to resolve these 2 possibilities. Interestingly, males tended to exhibit a greater propensity for lower bone density than females. Furthermore, all analyses presented are about prediction and correlation and as such cannot address causality.

Studies in mice harboring an LDS *Tgfbr1* allele known to cause severe disease in humans knocked into the endogenous genomic locus exhibited cortical, but not trabecular, bone abnormalities with decreased bone area, decreased cortical thickness, a diminished mineral apposition rate, and reduced mechanical strength.[23] Because the predominance of abnormalities were cortical, this has been proposed as the mechanism for the increased incidence of primarily appendicular fractures seen in some studies conducted on patients with LDS as opposed to spinal fractures that one would expect to be prevalent in a population with typical osteopenia reflected in a decreased DXA Z-score.[24] In our cohort, although only 4 patients had x-ray confirmed spinal compression fractures, this was almost one-quarter of those patients who had had spinal x-rays performed. Therefore, spinal fractures may be more common than previously thought; however, a study in which all patients underwent spinal x-rays would be necessary to conclusively answer this question.

All patients were screened for hyperparathyroidism as a cause for secondary osteopenia. One limitation of this study is that all patients were not also screened for other secondary causes of osteopenia, such as hyperthyroidism and celiac disease. Although we did not identify differences in DXA Z-scores across the different types of LDS, a second limitation is that there were limited numbers of patients with types 3, 4, and 5 LDS, and a larger sample size would be needed to make more definitive conclusions.

Although our data suggest that low bone mineral density is a defining characteristic of all forms of LDS, we observed a wide range of phenotypic severity. A number of clinical features were identified that predicted subsets of patients with LDS who were more likely to exhibit poor bone health. Allergic diseases are known to be more common among patients with types 1 and 2 LDS, but whether this is true in other forms of LDS is not yet clear. In our study, patients who had EGID exhibited lower DXA Z-scores than those without. This may reflect a subgroup of patients with more severe disease overall, those whose nutrition is adversely affected because of dietary restrictions, or those patients who may be receiving multiple courses of steroids, all of which can have a deleterious effect on bone strength. On further considering the contribution of allergic diseases, we found that a diagnosis of asthma was predictive of an increased number of fractures per year of life. As with EGID, this may reflect those with more severe disease but may also reflect repeated courses of steroids. We also saw a significant positive correlation between BMI and DXA Z-score. This suggests that better nutrition may lead to improved DXA Z-scores, although we cannot exclude the possibility that patients with low BMIs were more severely affected with comorbidities that independently had a negative impact on bone density. Because of

their underlying cardiovascular disease, patients with LDS are counselled to avoid contact sports, isometric exercises, and exercising to exhaustion. Although they are encouraged to participate in weight bearing activity despite these limitations, more severely affected individuals may have had less capacity to engage in physical activities.

Our analyses further suggest that subjects with >1 of 5 skeletal features (scoliosis, pes planus, arachnodactyly, spondylolisthesis, and camptodactyly) and especially children with > 2 skeletal features warrant close evaluation of bone health as these subgroups of patients with LDS are at highest risk for low bone density. Of these features, scoliosis and arachnodactyly may be most indicative of an underlying phenotype of low DXA Z-scores and a predilection toward fracture.

Human morphometric studies in LDS have been limited to a handful of bone biopsies. In 1 report, bone biopsy of a single patient with LDS showed an osteoblast dominant phenotype with thickened trabecular elements and an increased bone formation rate, although this patient had received several years of pamidronate infusions.[25] An iliac biopsy from 2 additional patients with LDS exhibited thin cortices, low trabecular bone volume, an elevated bone formation rate, elevated trabecular calcium content, and normal mineralization parameters. Bone resorption parameters were at or slightly below the reference range mean.[26] In contrast, measurement of serum bone turnover markers in our cohort of adult patients with LDS support an increase in bone resorption, which may have important therapeutic implications. Although previous data has been ambiguous on the role of bisphosphonates in LDS, with 1 patient responding to pamidronate infusions and another not responding well to zoledronic acid infusion,[26] our data shows an inverse correlation between CTX Z-score and whole-body DXA Z-score, suggesting that bisphosphonates might be an effective treatment for the bone phenotype in LDS. In this study, we describe 5 patients with LDS types 1 and 2 treated with bisphosphonates. All 5 patients had improvement in bone density in the forearm and femoral neck, whereas most improved in the total hip. Fewer responded positively in the spine and total body, although these regions could not be scored for some patients because of spinal hardware. As discussed, in mouse models the bone defect in LDS appears to be more apparent in cortical bone. This underlying pathophysiology may be why bisphosphonate treatment had a more apparent affect in the forearm and femur than in the spine and whole body.

This study presents evidence that a low DXA Z-score is a characteristic of all forms of LDS. Males with LDS appear to be more susceptible to low bone density in the spine than females, and those with EGID and allergic disease, including asthma, also appear to be at higher risk for poor bone health. Remarkably, the number of skeletal features a patient exhibits strongly predicts their likelihood of having a low DXA Z-score and fractures. Adults with >1 of 5 skeletal features and all children have lower whole-body DXA Z-scores than those who do not meet these criteria. Children with >2 skeletal features are especially at risk because they have whole-body DXA Z scores significantly < 2 SD below normal.

These findings highlight the importance of bone health monitoring and treatment in patients with LDS. We recommend that bone density assessment be performed as part of routine care in all patients with LDS. Patients should be counseled on dietary and lifestyle

interventions to optimize bone health, including maintaining adequate calcium and vitamin D intake,[27] promoting safe weight-bearing physical activity and avoiding additional risks such as smoking and alcohol use. Previous LDS management guidelines have suggested monitoring serum vitamin D periodically.[28] In particular, the relationship between low bone density and BMI in this study highlights the need to evaluate and optimize nutritional status in patients with LDS. Previous work has shown there is an increased prevalence of asthma and inflammatory disorders in LDS. Given the prevalence of low DXA Z-scores presented here, clinicians should be aware of the effect of steroids and other therapies on bone health. Clinicians should consider screening for vertebral compression fractures in at-risk and/or symptomatic patients using lateral spine imaging or DXA vertebral fracture assessment.[29] Although the decision to start treatment is multifactorial and should be made on a case-by-case basis, referral to a bone health specialist is appropriate for patients with low bone density and a history of fractures or who are at high risk for fracture-related morbidity. Bisphosphonates may be beneficial in some patients, although this requires further study to understand the safety and long-term benefit. A variety of formulations were used and were well-tolerated in this series. Clinicians should be cautious in prescribing oral bisphosphonates in patients with LDS given the known association with gastrointestinal disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Data Availability

Data will be supplied upon request.

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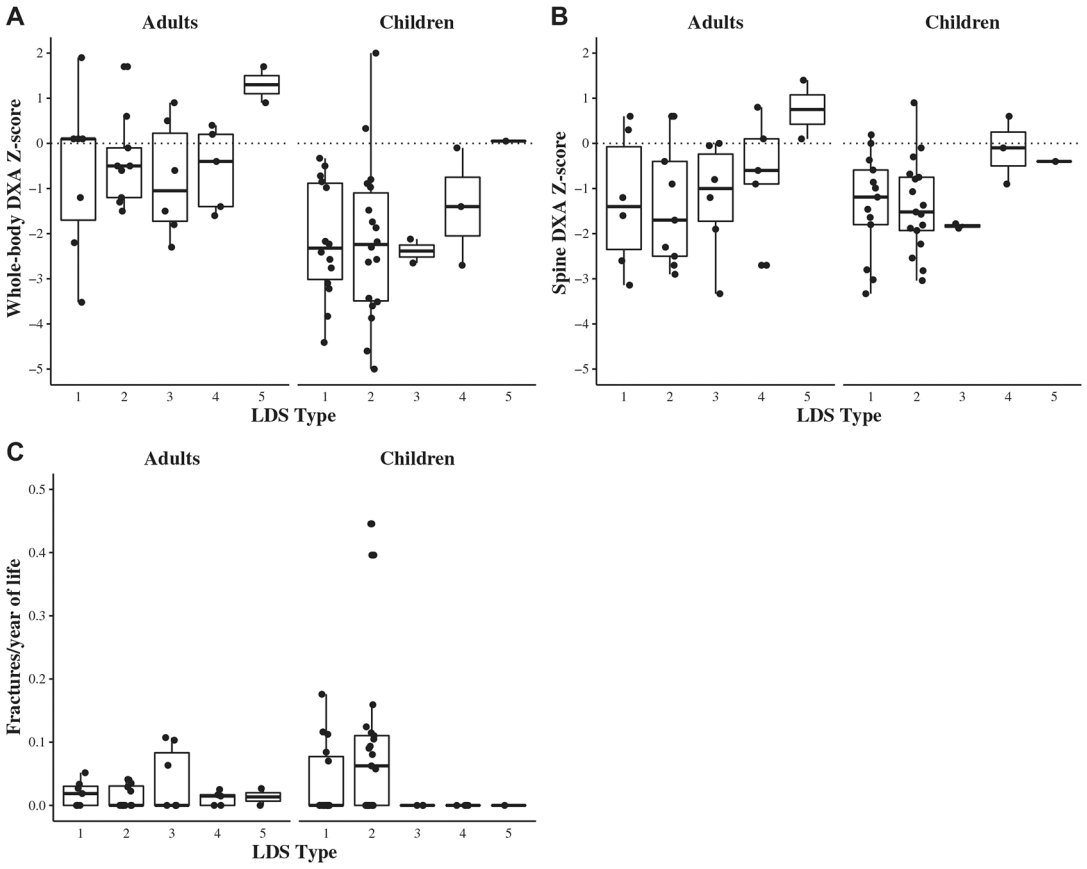

Figure 1. DXA scores and number of fractures in LDS types.

DXA Z-scores for the (A) whole-body and (B) spine according to the LDS type in adults and children. C. Number of fractures per year of life according to the LDS type in adults and children. DXA, dual-energy x-ray absorptiometry; LDS, Loeys–Dietz syndrome.

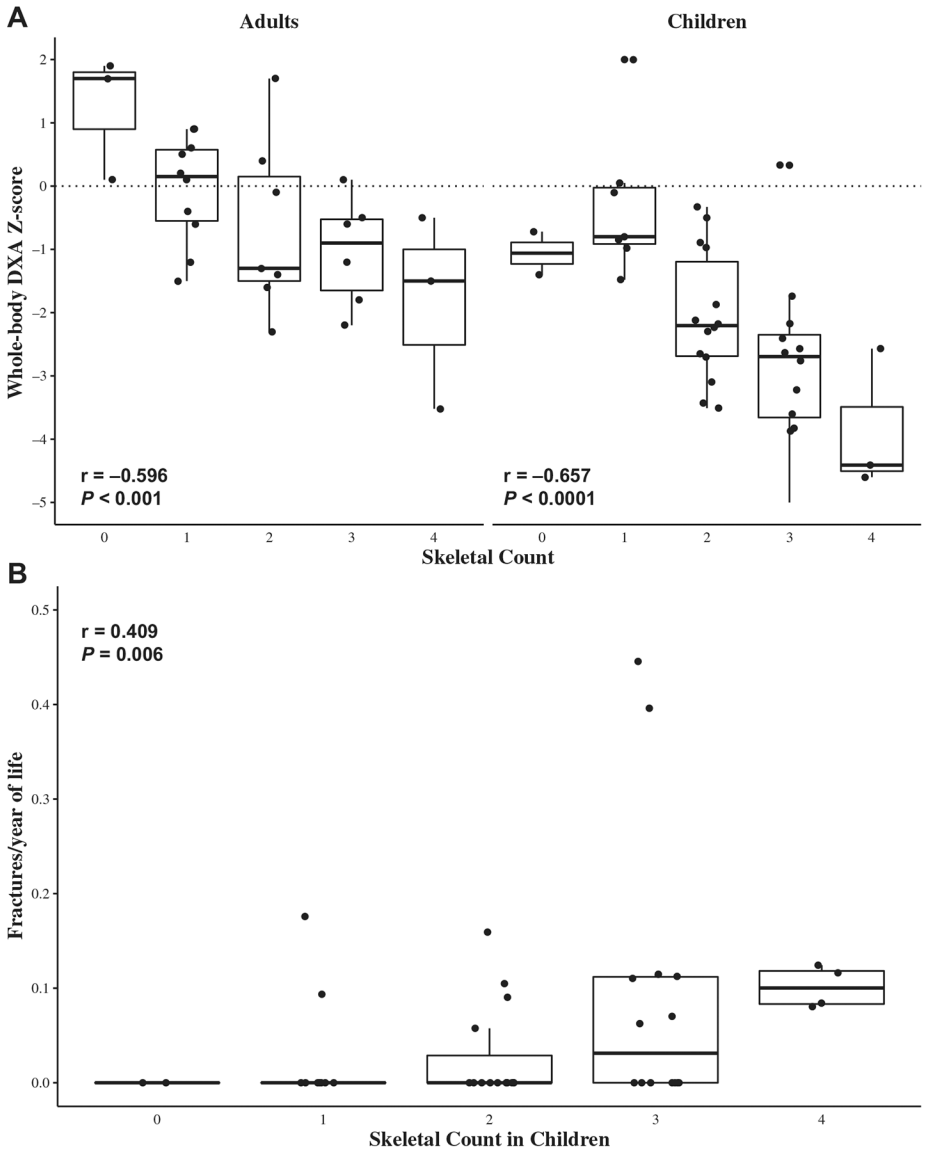

Figure 2. DXA scores and fractures/year by number of skeletal features.

A. Whole-body DXA Z-score by number of skeletal features (scoliosis, pes planus, arachnodactyly, spondylolisthesis, and camptodactyly) exhibited in each patient segregated by binary age. DXA Z-score is inversely correlated with the number of skeletal features for both adults and children (for adults, Spearman's r = −0.596, $P < .001$; for children, Spearman's r = −0.657, $P < .0001$). B. Fractures per year of life for children in relation to the number of skeletal features exhibited. Children with Loeys–Dietz syndrome show a positive correlation between the skeletal count and number of fractures per year of life (Spearman's r = 0.409, $P = .006$). DXA, dual-energy x-ray absorptiometry.

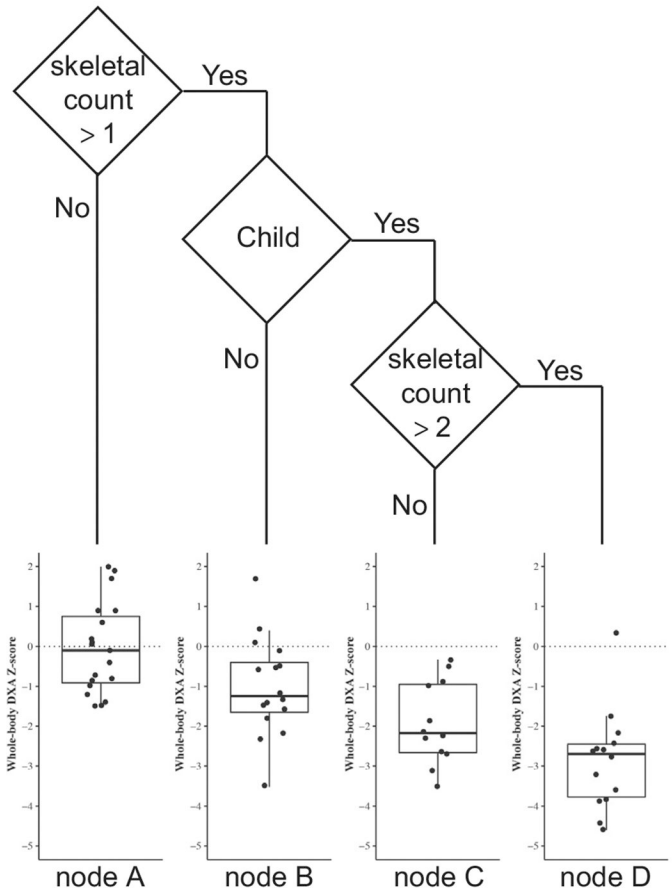

Figure 3. Decision tree analysis to determine which patients with Loeys–Dietz syndrome are most at risk for low whole body DXA Z-scores.

In this analysis, skeletal feature count (scoliosis, pes planus, arachnodactyly, spondylolisthesis, and camptodactyly) and binary age (adult vs child) were significant predictors of DXA Z-scores. The DXA Z-scores were significantly lower at each successive node (node A vs node B: $P = .016$, node B vs node C: $P = .027$, node C vs node D: $P = .0038$). Subjects in node A had whole-body DXA Z-scores that were normal and not significantly different than 0 ($P = .78$). DXA Z-scores of those in node B were significantly < 0 ($P = .008$) and those in node C were significantly < -1 ($P = .005$). For node D, the whole-body DXA Z-score was significantly < -2 ($P < .01$). DXA, dual-energy x-ray absorptiometry.

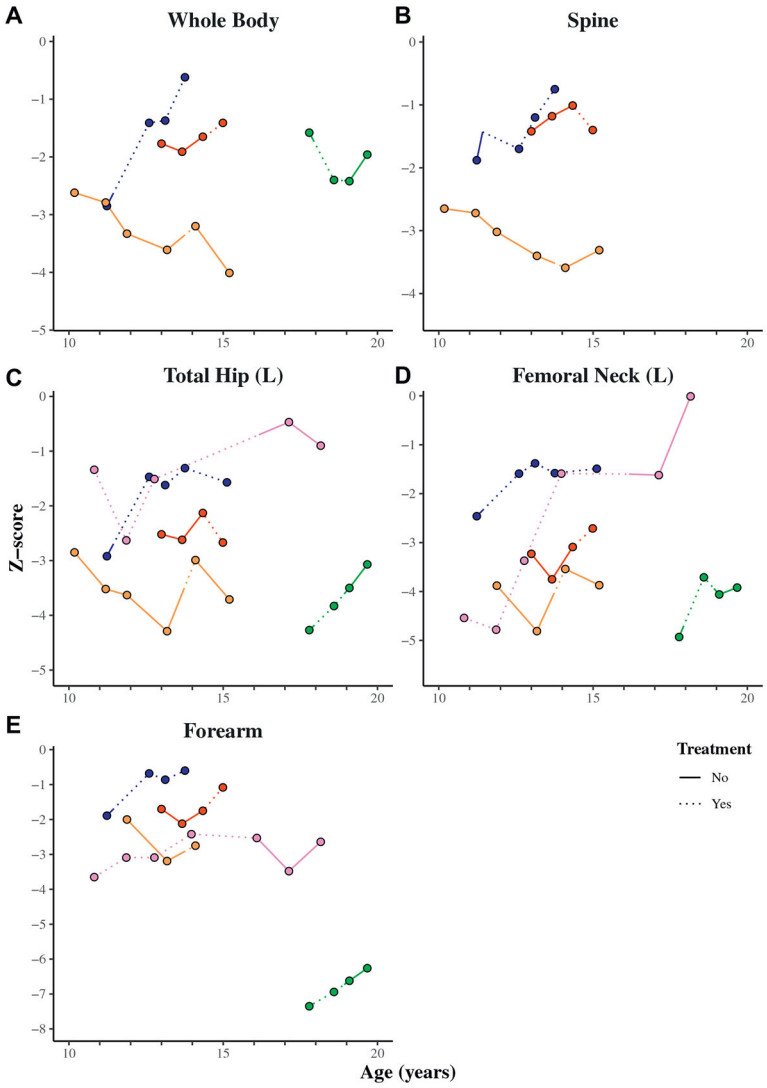

Figure 4. DXA Z-scores over time in patients receiving bisphosphonate infusions.

Dual-energy x-ray absorptiometry Z-score of the (A) whole body, (B) spine, (C) total hip, (D) femoral neck, and (E) forearm vs age for the 5 patients with Loeys–Dietz syndrome who received bisphosphonate infusions. Each patient is shown in a consistent color in the 5 graphs. Time when the patient was receiving a bisphosphonate infusion is shown as a dotted line. Time when the patient was not receiving infusions is shown as a solid line.

Table 1

Demographic data, laboratory data, and skeletal features of patients with a genetic diagnosis of LDS

	Overall ***N*** **= 77**	**Adults** ***n*** **= 33**	**Children** ***n*** **= 44**
LDS type 1	22 (28.6%)	7 (21.2%)	15 (34.1%)
LDS type 2	33 (42.9%)	12 (36.4%)	21 (47.7%)
LDS type 3	10 (13.0%)	7 (21.2%)	3 (6.8%)
LDS type 4	9 (11.7%)	5 (15.2%)	4 (9.1%)
LDS type 5	3 (3.9%)	2 (6.1%)	1 (2.3%)
Age	22.07 (17.38)	38.54 (14.20)	9.72 (4.42)
Male	31 (40.3%)	11 (33.3%)	20 (45.5%)
BMI (%)	20.26 (6.60)	25.73 (6.13)	16.17 (2.99)
Whole-body DXA Z-score[a]	−1.36 (1.62)	−0.45 (1.29)	−2.06 (1.50)
Spine DXA Z-score[b]	−1.17 (1.20)	−1.03 (1.37)	−1.27 (1.06)
P1NP Z-score (adults only)[c]		−0.08 (1.47)	
CTX Z-score (adults only)[c]		0.54 (1.34)	
Count of LDS skeletal features	2.87 (1.10)	2.67 (1.20)	3.02 (1.02)
Scoliosis	41 (53.2%)	18 (54.5%)	23 (52.3%)
Pectus deformity	42 (54.5%)	18 (54.5%)	24 (54.5%)
Pes planus	64 (83.1%)	24 (72.7%)	40 (90.9%)
Arachnodactyly	38 (49.4%)	14 (42.4%)	24 (54.5%)
Spondylolisthesis	4 (5.2%)	3 (9.1%)	1 (2.3%)
Cervical spine abnormalities	16 (20.8%)	4 (12.1%)	12 (27.3%)
Camptodactyly	16 (20.8%)	7 (21.2%)	9 (20.5%)

Continuous variables are presented as mean (SD). Categorical variables are presented as n (%)

BMI, body mass index; *CTX*, C-terminal telopeptide of type 1 collagen; *DXA*, dual-energy x-ray absorptiometry; *LDS*, Loeys–Dietz syndrome; *P1NP*, procollagen 1 intact N-terminal propeptide.

[a] Four adults and 6 children with missing data.

[b] Five adults and 8 children with missing data.

[c] Four adults with missing data.