Bone Fragility in EDS

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GLOBAL LEARNING CONFERENCE

Disclosures

- Medical advisor (volunteer) for:
  - Ehlers-Danlos Society
  - Hypermobile Syndromes Association (UK)
  - EDS UK
- Paid consultant for Resolys
- Speaker bureau:
  - Alexion Pharmaceuticals
- Author:
  - Joint Hypermobility Handbook
  - Issues and Management in Joint Hypermobility

EDS and Bone Fracture/Fragility

These RARE types of EDS are associated with bone fragility fractures

EDS Type	Genetic Defect	Characteristics
cEDS	*COL1A1* (R312C)	GJH; skin laxity; atrophic scaring; osteoporosis; aneurysm
Arthrochalasia	*COL1A1/2*	GJH; DDH
Dermatosporaxis	*ADAMTS2*	Dysmorphic features; blue sclerae; wide fontanel; extreme skin laxity and fragility
Kyphoscoliosis	*PLOD1*	Congenital scoliosis; GJH; DDH; hypotonia; marfanoid habitus
Brittle cornea syndrome	*ZNF469/PRDM5*	Dysmorphic features; SNHL; keratoconus/globus; GJH; DDH; blue sclerae; kyphoscoliosis
Spondylodysplastic	*B4GALT7/B3GALT6/SLC39A13*	Dysmorphic features; blue sclerae; bifid uvula; bone dysplasia

Brady A, et al. The Ehlers-Danlos syndromes, rare types. Am J Med Genet 2017;169C

PubMed Literature Search

- Search terms
  - EDS and osteoporosis
  - EDS and fracture
- 65 papers identified
  - 8 clinical case series/reports
  - 5 review
  - 7 rare EDS types
  - 7 not in English
  - 6 pre-1980
  - 28 not relevant

Coelho et al., 1994

- Assessed four patients with EDS I ages 16-25 by DXA

- No genetic data
- ?cEDS due to COL1A1 in #1

Deodhar and Woolf, 1994

- Described seven individuals with osteoporosis
- Majority were >50yoa
- All were diagnosed with EDS **after** their low bone density

- No further details

- Difficult to truly discern EDS >50
- One patient had blue sclerae
- No testing done

Deodhar and Woolf. Ehlers Danlos syndrome and osteoporosis. Ann Rheum Dis 1994;53:841-2

Dolan et al., 1998

- 23 adult (ages 18-64) cases of EDS (10 EDS I/II; 13 EDS III)
- Adjusted for functional status, age, height, weight, and gender
- Measured bone mineral density (BMD) and broad band ultrasound attenuation
- Lumbar BMD p=0.02; femoral neck BMD p=0.05; trochanter BMD p=0.02
  - 0.9 SD difference
- Any fractures: EDS= 78%; control 13% (P<0.001)
  - Majority were: 16 metatarsal (foot); 10 Colles' (wrist); 9 humerus
  - Lifetime fracture rate is 40% in England [BMJ, 2008]

Dolan AL, et al. Assessment of bone in Ehlers Danlos syndrome by ultrasound and densitometry. Ann Rheum Dis 1998;57:630-633.

Carbone et al., 2000

- 23 EDS III adults
- Femoral neck BMD was significantly reduced as compared to controls
- However once age, weight and activity-level were corrected for, the difference became not significant.

Gulbahar et al., 2006

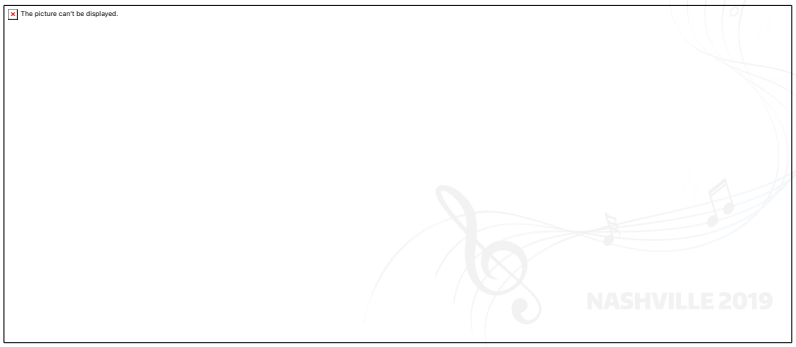
- Reduced BMD (mild osteopenia) in 23 premenopausal hypermobile women compared to controls by DXA at some sites but not others [Gulbahar et al., 2006].

Gulbahar S, et al. Hypermobility syndrome increases the risk for low bone mass. Clin Rheumatol 2006;25:511-514.

Yen et al., 2006

- Various types of EDS in 16 individuals (most clinical descriptions do not match type well), 11 of which had BMD
  - Reported as T-score not z-score
  - Many issues in clinical typing
  - No controls

Yen et al. Clinical features of Ehlers-Danlos syndrome. J Formos Med Assoc 2006;105:475-480.



Eller-Vainicher et al., 2016

- 50 consecutive cEDS/hEDS patients <50yoa
- Compared with age-, sex- and activity-matched controls
- Prevalence of osteoporosis was 10% in EDS v. 4% in controls
- Prevalence of asymptomatic vertebral fractures (radiologic marker-compression) was 10% in EDS and 0 in controls
  - "Fractured EDS patients showed similar… BMD"
- Lumbar vertebral fracture risk is highest in those that hyperextend (e.g. gymnasts, divers)
- Much greater fall frequency (>2 resulting in fracture) in EDS 8% as compared to 0%

Eller-Vainicher et al. Bone involvement in adult patients affected with Ehlers-Danlos syndrome. Osteoporosis Int 2016;8:2525-2531.

Mazziotti et al., 2016

- Cross-sectional study
- 52 EDS patients (all types; 12 cEDS; 37 hEDS) of all ages and 197 controls
- Measured BMD and occult vertebral fracture by morphometric analysis
- >50% of EDS patients had normal bone density (i.e. positive z-score)
- Only one (of 21 >50yoa) EDS patient had osteoporosis (compared to 19% controls)
- The marker for vertebral fracture more prevalent among EDS ($p<0.05$)
- "Patients with vertebral fractures showed no significant differences in age, sex, type of EDS, BMD and serum 25-hydroxyvitamin D values as compared to controls who did not fracture."

Mazziotti et al. High prevalence of radiologic vertebral fractures in adult patients with Ehlers-Danlos syndrome. Bone 2016;84:88-92

Holick et al., 2017

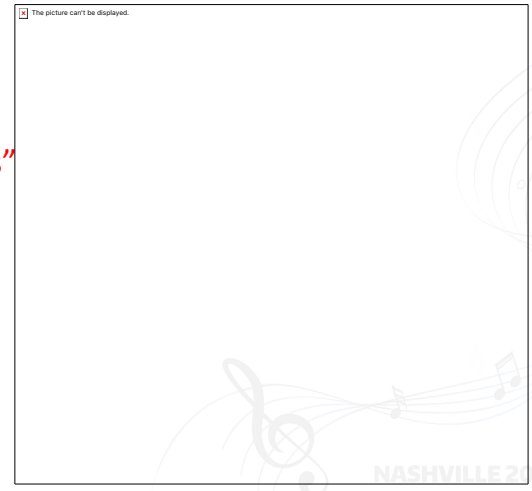
- Published in online journal; single peer-review; pay-to-publish; Holick editor

- 93% of infants had had clinical evidence of EDS
- **Only family members (not infants) were evaluated in 36%**
  - 61% had multiple rib fractures
  - 39% long bone fracture
  - 13% skull fracture
  - Many with fractures at various stages of healing

Holick MF, et al. Multiple fractures in infants who have Ehlers-Danlos/hypermobility syndrome and or vitamin D deficiency: a case series of 72 infants whose parents were accused of child abuse and neglect. Dermato-Endocrinology 2017;9:1.

Holick et al., 2017 (2)

- Used Beighton ≥5 score to define GJH
- Used only GJH to diagnose EDS
  - "most were not aware they had this"
- 65% screened for OI
  - 4% found to have causative variant in *SERPINF1* (OI VI)
    - Diagnosed with OI/EDS overlap
- 27/47 (63%) reportedly had vitamin D deficiency (<20ng/ml)



Rolfes et al. 2019

- Retrospective, population-based, case-control study identified subjects with EDS from 1976 to 2015 who had complete records for at least their first year of life.
- Diagnosis used the 2017 International Classification of the Ehlers-Danlos Syndromes.
- Records were reviewed for fracture diagnoses that were characterized by age, location, type and mechanism.
- Of 219 potential cases, 21 had complete records for the first year of life and sufficient evidence in the medical record to support an EDS diagnosis.
  - Of these 21, there were 14 hypermobile, 2 classical, 4 vascular, and 1 arthrochalasia EDS subtypes.
  - 11 of 21 EDS cases (52.4%) and 15 of 63 controls (23.8%) had one or more fractures during childhood.
  - **No fractures were identified in the first year of life.**
  - Comparing cases to controls, EDS was associated with having any fractures during childhood with an odds ratio of 3.4 (95% CI: 1.20-9.66).
- "We found no evidence that infants with common forms of EDS are predisposed to more frequent fractures. Ambulatory subjects with these EDS subtypes may have a higher incidence of fractures during childhood."

Rolfes MC. Et al. Fracture incidence in Ehlers-Danlos syndrome- A population-based case-control study. Child Abuse Negl. 2019;91:95-101.

Conclusion

- Evidence of reduced bone mass in rare types of EDS
- Lack of consistent and reliable evidence of reduced bone mass in classic or hypermobile EDS
- There have been no substantive published reports substantiating hEDS or cEDS as the cause for infantile fractures in the setting of suspected nonaccidental trauma (child abuse)
- Such persons should be evaluated for other underlying disorders as outlined in the American Academy of Pediatrics Guideline [Flaherty et al., 2014].

Castori M. Ehlers-Danlos syndrome(s) mimicking child abuse: is there an impact on clinical practice? Am J Med Genet C 2015;169C:289-292.
Hickey SE, Moran RT, Tinkle BT. A review of generalized joint hypermobility in infants and children: Differential diagnosis and recommendations for management. A clinical practice resource of the American College of Medical Genetics and Genomics. Genet Med 2017.
Tinkle B, et al. Hypermobile Ehlers-Danlos Syndrome (a.k.a. Ehlers-Danlos Syndrome Type III and Ehlers-Danlos syndrome hypermobility type): Clinical Description, and Natural History. Am J Med Genet 2017;169C

The Ehlers Danlos Society

GLOBAL LEARNING CONFERENCE NASHVILLE 2019

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NASHVILLE 2019

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New ICD-10 CODES!!!!!!!!!!!!!!!!!

- Delete: Q796 Ehlers-Danlos syndrome
  Add: Q7960 Ehlers-Danlos syndrome, unspecified
  Add: Q7961 Classical Ehlers-Danlos syndrome
  Add: Q7962 Hypermobile Ehlers-Danlos syndrome
  Add: Q7963 Vascular Ehlers-Danlos syndrome
  Add: Q7969 Other Ehlers-Danlos syndromes

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