



Increased Opioid Use in Patients with Ehlers-Danlos Syndrome Before and After Total Hip Arthroplasty

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Disclosures

The authors have no pertinent disclosures related to the content or topic in this presentation

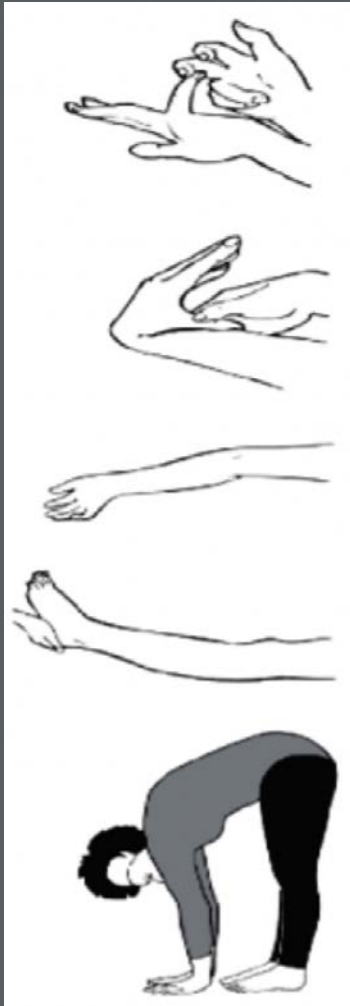
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Objectives

- 1) Understand the basic pathophysiology of Ehlers-Danlos Syndrome and its complex pain manifestations
- 2) Learn how Ehlers-Danlos Syndrome may affect total hip arthroplasty outcomes
- 3) Appreciate how multidisciplinary care may play a critical role in management of patients with Ehlers-Danlos Syndrome

Background: Ehlers-Danlos Syndrome



- Ehlers-Danlos Syndrome (EDS) is a spectrum of disorders encompassing abnormal collagen synthesis¹
- Incidence of 1 in 5,000^{2,3}
- 75% of patients with EDS present with symptoms by 15 years old⁴
- Six subtypes of varying hereditary patterns¹
- Classically includes: joint hypermobility, skin hyperextensibility, poor wound healing, CV, GI, neurologic manifestations^{1,5-9}
- MSK complaints: joint pain, swelling, hyperlaxity → joint microtrauma and osteoarthritis (OA)^{7,10,11}
- Diagnostic criteria: Beighton Score + clinical^{6,7}

Image from: <https://mediphysio.com.au/hypermobility/>

Background: EDS and Chronic Pain

- Hypermobile Type most common, chronic pain in 90%¹²
- Multiple organ system manifestations → difficulty with pain control
- Opioid use challenging given decreased GI motility, postural orthostatic tachycardia, dysautonomia, proprioceptive deficits^{12,13}
- Prolonged opioid → central pain sensitization¹⁴⁻¹⁶
- Opioids not indicated for EDS-related chronic MSK pain, reserved for acute exacerbations or refractory pain^{4,17}

Image from: <https://pdb101.rcsb.org/motm/4=>

Current Literature

EDS and Total Hip Arthroplasty (THA):

- EDS patients undergoing hip arthroscopy for hip pain/instability show persistent femoroacetabular impingement, extreme capsular laxity → earlier indications for THA¹⁰
- EDS patients are at increased risk for dislocation and revision^{18,19}

What Remains Unknown:

- Opioid use in patients with EDS undergoing THA pre- and post-operatively
- Effect of opioid use on THA outcomes in the EDS population

Purpose

- Primary: investigate opioid use in patients with EDS undergoing THA
- Secondary: determine post-operative risks associated with opioid use in the EDS population following THA

Methods



Design

Cohort

Outcome Variables

Statistics

Retrospective review

2015-2020

Demographics

Descriptive statistics

PearlDiver Database

Patients with EDS

Prior hip arthroscopy

Continuous variables t-tests

International Classification of Disease, tenth revision codes

Ages 45-75

Dislocation, infection, revision, medical complications

Categorical variables Chi-square tests

Primary THA for OA

Propensity matched population control based on age, sex, obesity

Opioid prescription (Rx), morphine milliequivalent dosing (mme) at 90 days before, 90 days after, 365 days after THA

Multivariate analysis

Population

25,688 patients with EDS diagnosis

238 EDS patients underwent THA for OA

Propensity matched control population of 1,244,368



	Pre-propensity matching				Post-propensity matching		
	EDS	Control	Standard deviation	Variation ratio	Propensity matched control	Standard deviation	Variation ratio
Age (years)	54.31	50.78	0.43	0.26	54.31	0.00	1.00
Sex F	0.84	0.59	0.69	N/A	0.84	0.00	N/A
Sex M	0.16	0.41	-0.69	N/A	0.16	0.00	N/A
Obesity	0.30	0.24	0.13	N/A	0.31	0.00	N/A

Results

Patients with EDS were more likely to undergo THA

OR 1.82, $p < 0.0001$

More likely to have previous hip arthroscopy

6.7% vs. 0.6%, OR 12.5, $p < 0.0001$

More likely to use opioids

90 days pre-op: 49.1% vs. 35.0%, OR 1.78, $p < 0.0001$

90 days post-op: 59.7% vs. 40.9%, OR 2.08, $p < 0.0001$

Consumed higher quantity of opioids

90 days pre-op: 1163.6 mme \pm 1562.8 vs 731.9 mme \pm 1230.7, $p < 0.0001$, Cohen's d = 0.31

90 days post-op: 900.1 mme \pm 1235.9 vs 651.7 mme \pm 1150.9, $p < 0.0001$, Cohen's d = 0.21

Results

Patients with EDS were less likely to be short-term opioid users, more likely to have prolonged opioid course

Short term: 39.1% for EDS patients compared to 60.5% for controls, OR 0.45, $p < 0.0001$

Long term: 50.8% for EDS patients, 31.0% for controls, OR 2.17, $p < 0.0001$

If using opioids pre-operatively, more likely to use opioids post-op

90 days post-op: OR 8.19, CI 4.47-15.02

365 days post-op: OR 4.93, CI 2.84-8.53

If using opioids 90 days post-op, then more likely to dislocate

OR 8.16, CI 1.87-35.66

No difference in revision, infection, medical complications between opioid users and non-opioid users with EDS pre-op or post-op

Discussion

- Higher levels of opioid use among patients with EDS in arthroplasty
- EDS patients are more likely to consume opioids and use greater amounts before and after THA
- EDS patients are less likely to discontinue opioid use post-operatively
- Opioid use associated with increased dislocation risk

Discussion – Pain

- Retrospective study by Song et al.²⁰
 - EDS patients most likely to pursue complimentary/alternative medicine (89.7%) followed by opioid and opioid-like pain medications (88.8%)
 - 40% of patients with EDS report improvement in pain with opioids, 22% report adverse symptoms
 - Most effective treatment was bracing (70%)
- In THA EDS population, high likelihood of persistent opioid use at one year post-op
- Consider engaging pain specialist for long-term pain control

Discussion – Dislocation

- Recent PearlDiver study by Moore, et al. of 365 patients with EDS undergoing THA found:¹⁸
 - Significantly higher periprosthetic dislocation at 90-days postop (4.2% vs 1.7%, $p = 0.001$)
 - At 5-years post-op, 10.3% with EDS, 3.3% of matched group
 - EDS with lower revision-free survivorship, 92.7% implant survival at five years versus 96.1% matched ($p = 0.004$)
- Our study shows heightened dislocation risk associated with opioid use at 90-days postop
- Further study regarding economic impact needed

Limitations

- Retrospective database study
- Coding bias
- Variety of phenotypes within EDS spectrum
- Unable to assess concurrent or alternative analgesic use or other analgesic strategies
- Opioid use estimation based on Rxs
- Possible multifactorial etiology of pain leading to opioid use

Conclusions

Elevated risk of opioid use both pre- and post-op should be taken into account when advising patients with EDS who are considering THA

Patients who persistently consume opioids post-operatively may be at heightened risk for dislocation

Recommend counseling regarding opioid use, consideration of a multi-disciplinary approach to discuss alternative analgesic modalities



Thank You

References

1. Mao JR, Bristow J. The Ehlers-Danlos syndrome: on beyond collagens. *J Clin Invest*. 2001;107(9):1063-1069.
2. Malfait F, Francomano C, Byers P, et al. The 2017 international classification of the Ehlers-Danlos syndromes. *Am J Med Genet C Semin Med Genet*. 2017;175(1):8-26. doi:10.1002/ajmg.c.31552
3. Demmler JC, Atkinson MD, Reinhold EJ, Choy E, Lyons RA, Brophy ST. Diagnosed prevalence of Ehlers-Danlos syndrome and hypermobility spectrum disorder in Wales, UK: a national electronic cohort study and case-control comparison. *BMJ Open*. 2019;9(11):e031365. doi:10.1136/bmjopen-2019-031365
4. Gazit Y, Jacob G, Grahame R. Ehlers-Danlos Syndrome-Hypermobility Type: A Much Neglected Multisystemic Disorder. *Rambam Maimonides Med J*. 2016;7(4):e0034. doi:10.5041/RMMJ.10261
5. Germain DP. Clinical and genetic features of vascular Ehlers-Danlos syndrome. *Ann Vasc Surg*. 2002;16(3):391-397. doi:10.1007/s10016-001-0229-y
6. Beighton P. Ehlers-Danlos syndrome. *Ann Rheum Dis*. 1970;29(3):332-333. doi:10.1136/ard.29.3.332
7. Beighton P, Horan F. Orthopaedic aspects of the Ehlers-Danlos syndrome. *J Bone Joint Surg Br*. 1969;51(3):444-453.
8. Atzinger CL, Meyer RA, Khoury PR, Gao Z, Tinkle BT. Cross-sectional and longitudinal assessment of aortic root dilation and valvular anomalies in hypermobile and classic Ehlers-Danlos syndrome. *J Pediatr*. 2011;158(5):826-830.e1. doi:10.1016/j.jpeds.2010.11.023
9. Fikree A, Chelimsky G, Collins H, Kovacic K, Aziz Q. Gastrointestinal involvement in the Ehlers-Danlos syndromes. *Am J Med Genet C Semin Med Genet*. 2017;175(1):181-187. doi:10.1002/ajmg.c.31546
10. Larson CM, Stone RM, Grossi EF, Giveans MR, Cornelsen GD. Ehlers-Danlos Syndrome: Arthroscopic Management for Extreme Soft-Tissue Hip Instability. *Arthroscopy*. 2015;31(12):2287-2294. doi:10.1016/j.arthro.2015.06.005
11. Stanitski DF, Nadjarian R, Stanitski CL, Bawle E, Tsipouras P. Orthopaedic manifestations of Ehlers-Danlos syndrome. *Clin Orthop Relat Res*. 2000;(376):213-221. doi:10.1097/00003086-200007000-00029
12. Scheper MC, de Vries JE, Verbunt J, Engelbert RH. Chronic pain in hypermobility syndrome and Ehlers-Danlos syndrome (hypermobility type): it is a challenge. *J Pain Res*. 2015;8:591-601. doi:10.2147/JPR.S64251
13. De Wandele I, Rombaut L, Malfait F, De Backer T, De Paepe A, Calders P. Clinical heterogeneity in patients with the hypermobility type of Ehlers-Danlos syndrome. *Res Dev Disabil*. 2013;34(3):873-881. doi:10.1016/j.ridd.2012.11.018
14. Zhou Z, Rewari A, Shanthanna H. Management of chronic pain in Ehlers-Danlos syndrome: Two case reports and a review of literature. *Medicine (Baltimore)*. 2018;97(45):e13115. doi:10.1097/MD.00000000000013115
15. Chopra P, Tinkle B, Hamonet C, et al. Pain management in the Ehlers-Danlos syndromes. *Am J Med Genet C Semin Med Genet*. 2017;175(1):212-219. doi:10.1002/ajmg.c.31554
16. Ericson WB, Wolman R. Orthopaedic management of the Ehlers-Danlos syndromes. *Am J Med Genet C Semin Med Genet*. 2017;175(1):188-194. doi:10.1002/ajmg.c.31554
17. Tinkle B, Castori M, Berglund 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 C Semin Med Genet*. 2017;175(1):48-69. doi:10.1002/ajmg.c.31538
18. Moore HG, Burroughs PJ, Rubin LE, Frumberg DB, Sculco PK, Grauer JN. Patients With Ehlers-Danlos Syndromes Experience Higher Rates of Prosthetic Dislocation After Total Hip Arthroplasty and Worse Implant Survival at 5 Years. *J Am Acad Orthop Surg*. 2022;30(4):177-183. doi:10.5435/JAAOS-D-21-00347
19. Guier C, Shi G, Ledford C, Taunton M, Heckman M, Wilke B. Primary Total Hip Arthroplasty in Patients With Ehlers-Danlos Syndrome: A Retrospective Matched-Cohort Study. *Arthroplast Today*. 2020;6(3):386-389. doi:10.1016/j.artd.2020.05.006
20. Song B, Yeh P, Nguyen D, Ikpeama U, Epstein M, Harrell J. Ehlers-Danlos Syndrome: An Analysis of the Current Treatment Options. *Pain Physician*. 2020;23(4):429-438.