5-year Fracture Rate among Transgender Patients Using Gender-affirming Hormone Therapy

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INTRODUCTION: An estimated 1.6 million people living in the United States identify as transgender or gender diverse (TGD), having a gender identity different from their sex assigned at birth.[1] TGD patients have unique health care needs related to the use of gender-affirming hormone therapy (GAHT). For adult patients, the World Professional Association for Transgender Health (WPATH) defines GAHT as a medically necessary treatment regimen based on either estrogen (17-B estradiol with anti-androgen therapy) or testosterone. [2, 3] GAHT acts via increasing secondary sex characteristics congruent with a patient's gender identity, while simultaneously reducing unwanted secondary sex characteristics.[2, 3] Data suggests that up to 80% of TGD patients either currently use or intend to use GAHT for gender affirmation [4]. GAHT is associated with reductions in mental health burden and improved quality of life, and many patients use this therapy long-term.[2, 5] Given the importance of estrogen and testosterone in lifelong bone health maintenance, GAHT's influence on bone density is an active area of research. The largest and most recent review and meta-analysis of adults undergoing long-term GAHT found either neutral or positive direct effects on BMD.[6] Data has shown rates of low bone mineral density (BMD) in TGD patients assigned male at birth (AMAB) prior to hormone initiation range from 12.9% - 40%, but this trend is not seen in TGD patients assigned female at birth (AFAB).[7-9] A paucity of data, however, describes resultant fracture risk associated with GAHT, the most clinically relevant outcome of low BMD.[10] The primary objective was to assess if GAHT was associated with 5-year fracture rate.

METHODS: All work was approved by an IRB. Using the Truven MarketScan Commercial Claims database from 01/01/2009 to 12/31/2019, we conducted a retrospective cohort analysis of de-identified TGD patients aged 18 – 65 years old and without claims-based evidence of bone disease or active malignancy. TGD patients were identified from 01/01/2009 to 12/31/2014 to allow for a 5-year follow-up. For patient identification, we used International Classification Database, Ninth and Tenth Revision (ICD-9/ICD-10) gender identity diagnosis codes previously described in other studies.[11, 12] GAHT was identified via claims for relevant national drug codes based on generic name and formulation, and included use of Estrogen-based GAHT (EGAHT) including 17-B estradiol with anti-androgen therapy (spironolactone, finasteride, dutasteride) or testosterone-based GAHT (TGAHT) with testosterone.[5] An intention-to-treat design was used for GAHT cohorts. Those not using GAHT were assessed as a non-GAHT comparison cohort. Patients excluded from analysis included those using gonadotropin releasing hormone analog (GnRHa), anti-androgen therapy alone or use of estrogen alone. Start of follow up (i.e. day 0) was based on the date of GAHT initiation for EGAHT and TGAHT cohorts or the first available enrollment date for the non-GAHT cohort. The first date of fracture (hip, vertebral, upper extremity, lower extremity) following day 0 was identified using inpatient or outpatient fracture claims through 12/31/2019 based on previously demonstrated fracture modeling.[13] The incidence rate (IR per 1000 person years) of 5-year fracture was estimated for each cohort. Cox proportional hazards regression estimated the hazard ratio ([HR] with 95% confidence interval [CI]) of 5-year fracture comparing the cohorts after adjusting for age. Individuals were followed until the date of their first fracture event, loss of continuous health plan enrollment or end of the 5-year follow-up, whichever came first. We tested for effect modification by age (as continuous). SAS version 9.4 was used to conduct all analysis.

RESULTS: Among TGD patients (n=11,953), the IR of fracture was 14.3 (95% CI 10.9 – 17.7) for EGAHT (n=2,282), 17.3 (95% CI 13.4 – 21.2) for TGAHT (n=1,963) and 20.8 (95% CI 18.9 – 22.3) for non-GAHT (n=7,708). Most fractures occurred at the foot (28%), followed by the hand (26%) and ankle (13%). Compared to non-GAHT, the age-adjusted HR was 0.83 (95%CI=0.63 – 1.10) for TGAHT and 0.72 (95%CI=0.54 – 0.95) for EGAHT. Compared to EGAHT, the age-adjusted HR was 0.42 (95%CI=0.81 – 1.67) for TGAHT. There was no evidence of effect modification by age (*p* for interaction, 0.875).

DISCUSSION: These results suggest that EGAHT and TGAHT were associated with a lower 5-year all-cause fracture rate compared to TGD patients not on GAHT, although, only EGAHT reached statistical significance. The study also found no evidence of effect modification by age, suggesting that the strength of the associations was similar across the 18–65-year-old age range. We hypothesize that the bone enhancing effects of estrogen may play a role in reducing the 5-year fracture rate. A major strength of this study was the relatively long 5-year follow-up period, which allowed us to capture incident fracture rates within a clinically meaningful period. One limitation was that it was not examined whether GAHT cohorts continued therapy throughout the duration of their follow-up period. Future studies could use an on-treatment design that quantifies associations based on cumulative GAHT exposure. A second limitation was that the study design did not account for confounding. A final limitation includes the TGD non-GAHT group which was not able to be separated by sex/gender, since the "patient sex" identifier is an unreliable indicator of sex assigned at birth for TGD patients. Future research is needed to confirm these associations. Furthermore, given that the long-term clinical use of GAHT, longer-term fracture incidence studies will be important for future evaluation.

SIGNIFICANCE/CLINICAL RELEVANCE: Population-level fracture data is required to guide appropriate patient counseling on bone health maintenance throughout the lifespan. In this study, we leveraged the power of claims data, finding a lower fracture incidence in TGD patients using EGAHT.

REFERENCES: (1) Herman JL et al., *"How many Adults and Youth Identify as Transgender in the United States?"* 2023. (2) Coleman et al., DOI: 10.1080/26895269.2022.2100644 (3) Hembree et al., DOI: 10.1210/jc.2017-01658 (4) Grant, J. M. M. L., et al. *"National transgender discrimination survey report on health and health care."* 2010. (5) Baker et al., DOI: 10.1210/jendso/bvab011 (6) Singh-Ospina et al., DOI: 10.1210/jc.2017-01642 (7) Radix A, Deutsch M. *"Bone Health and Osteoporosis"*. https://transcare.ucsf.edu/guidelines/bone-health-and-osteoporosis. (8) Motta et al., DOI:10.1007/s00774-020-01127-9 (9) Van Caenegem E, T'Sjoen G. DOI: 10.1097/MED.0000000000000202 (10) Wiepjes et al., 2020 DOI: 10.1002/jbmr.3862 (11) Proctor et al., DOI: 10.1089/trgh.2016.0031 (12) Singer et al., DOI: 10.1007/s11657-023-01229-7 (13) Whitney, D. 10.1038/s41390-022-02207-4

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IMAGES AND TABLES: