



Transgender Medicine and Bone Health

2021 Interdisciplinary Symposium on Osteoporosis (ISO2021)

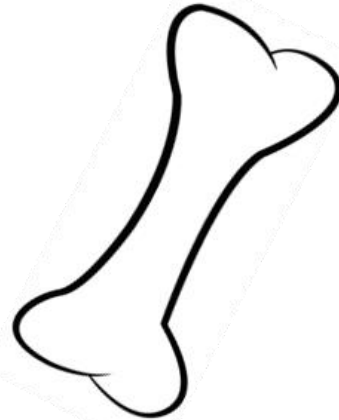
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University of California, San Francisco

13 May 2021



Disclosures

- No relevant conflicts of interest for this talk
 - I have served on advisory boards for Ultragenyx Pharmaceuticals
- I will be discussing non-FDA approved therapies

Roadmap

- Background & Brief Review: Gender
- Current Literature & Approach: Pediatrics
- Current Literature & Approach: Adults
- Summary & Future Directions
- Questions



Background: Let's Talk About Gender

Setting the Stage with the Lingo

- **SEX: male/female/intersex**
 - Assigned/designated/recorded at birth, birth-assigned/designated/recorded
- **GENDER: Affirmed gender / gender identity (exists on a spectrum)**
 - Binary
 - Transgender boy/man (female-to-male, transmasculine, trans man) & cisgender boy/man
 - Transgender girl/woman (male-to-female, transfeminine, trans woman) & cisgender girl/woman
 - Non-Binary
 - Agender, gender queer, gender fluid, non-binary transmasculine/transfeminine spectrum
- **Gender non-conforming/diverse/expansive/creative**
- **Transgender and Gender Diverse (TGD)**

Background: Gender Dysphoria

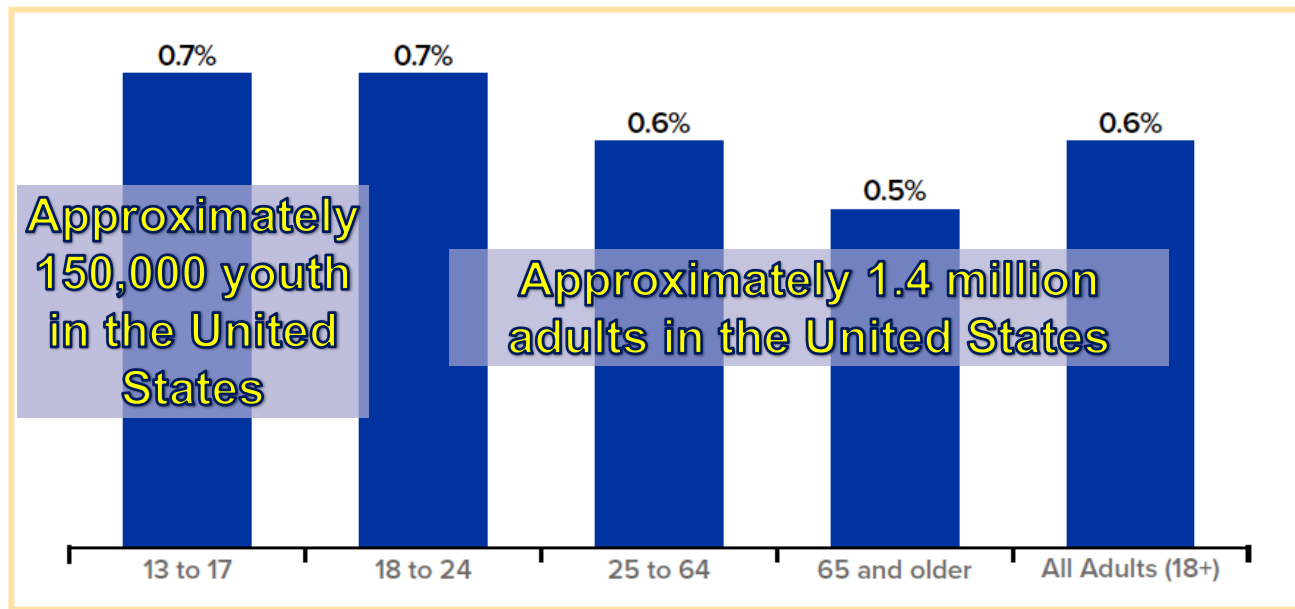
Diagnostic Criteria

- Recognized in the newest 2013 edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM)-V, defined as:
 - Marked difference between person's expressed/experienced gender & gender others would assign
 - Persist for at least 6 months
 - Children must verbalize this desire
 - Condition causes significant distress or impairment in functioning
- Previously known as "Gender Identity Disorder" in DSM-IV

Estimated Population in the United States

The Williams Institute – January 2017

Figure 1. Percentage of Individuals Who Identify as Transgender by Age



Using local probability surveys and national convenience samples %youth who identified as transgender ranged from **1.3% to 3.2%**.

Wilson BDM, Kastanis A. (2015). Sexual and gender minority disproportionality and disparities in child welfare: A population-based study. *Children and Youth Services Review*, 58, 11-17.
Johns MM, et al. (2019). Transgender Identity and Experiences of Violence Victimization, Substance Use, Suicide Risk, and Sexual Risk Behaviors Among High School Students — 19 States and Large Urban School Districts, 2017. *MMWR*, 69(3):67-71.

Herman JL, Flores AR, Brown TNT, Wilson BDM, Conron KJ. (2017). *Age of Individuals Who Identify as Transgender in the United States*. Los Angeles, CA: The Williams Institute.

⁶ Flores AR, Herman JL, Gates GJ, Brown TNT. (2016). *How Many Adults Identify as Transgender in the United States?* Los Angeles, CA: The Williams Institute.

Gender-Affirming Care of TGD Youth

United States – Brief History

- First described in the literature ~2007 – Boston Children's Hospital "Gender Management Service" (GeMS)
- 01/2009 – At UCSF, Dr. Steve Rosenthal treated his first pediatric TGD patient
- 09/2009 – The Endocrine Society publishes first Clinical Practice Guidelines focused on endocrine treatment of "transsexual" persons
- 05/2012 – The UCSF Child and Adolescent Gender Center (CAGC) – multidisciplinary clinic was formed

Treatment Approach

DSM-V Gender Dysphoria (2013)

Mental Health Gender Specialist

Early
Childhood

Late
Childhood/Pre
-Puberty

Early Puberty

Late Puberty

Adulthood

School Resources,
Social Transition

Puberty
Blockers:
GnRH
agonists

Gender-Affirming
Sex Hormones

Surgeries



TESTOPEL[®]
(testosterone pellets)



Fertility
Preservation



The “Dutch treatment protocol”

Featured prominently in first iteration of Endocrine Society guidelines

- Puberty blockers after puberty starts
- Gender-affirming sex hormones initiated at 16 years (age of majority in The Netherlands)
- 2017 revised guidelines - updated language to suggest gender-affirming sex hormones could be initiated earlier (without specific recommended ages)

Gender-Affirming Medical Therapies

For TGD Youth – peer-concordant puberty timing model

- Puberty Blockers (GnRH agonists)
 - Eligible at Tanner Stage 2 of puberty
 - At UCSF, no monotherapy beyond 14 years
- Gender-Affirming Sex Hormones (Estrogen or Testosterone)
 - Timing of initiation is controversial!
 - At UCSF, had been around 14 years but often earlier
 - Practice dependent, but guidelines suggest hard limit of 16 years
- Other Medications (spironolactone, bicalutamide, etc)

Clinical Practice Guidelines

The Endocrine Society, UCSF Center of Excellence for Transgender Health, World Professional Association for Transgender Health

International Journal of Transgenderism, 13:165–232, 2011
Copyright © World Professional Association for Transgender Health
ISSN: 1553-2739 print / 1434-4599 online
DOI: 10.1080/15532739.2011.700873



Standards of Care for the Health of Transsexual, Transgender, and Gender-Nonconforming People, Version 7

Coleman, E., Bockting, W., Botzer, M., Cohen-Kettenis, P., DeCuypere, G., Feldman, J., Fraser, L., Green, J., Knudson, G., Meyer, W. J., Monstrey, S., Adler, R. K., Brown, G. R., Devor, A. H., Ehrbar, R., Ettner, R., Eyler, E., Garofalo, R., Karasic, D. H., Lev, A. I., Mayer, G., Meyer-Bahlburg, H., Hall, B. P., Pfaefflin, F., Rachlin, K., Robinson, B., Schechter, L. S., Tangpricha, V., van Trotsenburg, M., Vitale, A., Winter, S., Whittle, S., Wylie, K. R., & Zucker, K.

Guidelines for the Primary and Gender-Affirming Care of Transgender and Gender Nonbinary People

Center of Excellence for Transgender Health

Department of Family & Community Medicine

University of California, San Francisco

2nd Edition – Published June 17, 2016

Editor - Madeline B. Deutsch, MD, MPH

Endocrine Treatment of Gender-Dysphoric/ Gender-Incongruent Persons: An Endocrine Society* Clinical Practice Guideline

Wylie C. Hembree,¹ Peggy T. Cohen-Kettenis,² Louis Gooren,³ Sabine E. Hannema,⁴ Walter J. Meyer,⁵ M. Hassan Murad,⁶ Stephen M. Rosenthal,⁷ Joshua D. Safer,⁸ Vin Tangpricha,⁹ and Guy G. T'Sjoen,¹⁰

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***Cosponsoring Associations:** American Association of Clinical Endocrinologists, American Society of Andrology, European Society for Pediatric Endocrinology, European Society of Endocrinology, Pediatric Endocrine Society, and World Professional Association for Transgender Health.

Coleman E, Bockting W, Botzer M, et al. Standards of Care for the Health of Transsexual, Transgender, and Gender-Nonconforming People, Version 7. *International Journal of Transgenderism*. 2012;13(4):165-232.

11 Hembree WC, Cohen-Kettenis PT, Gooren L, et al. Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2017;102(11):3869-3903



Bone Mass in Young Adulthood Following Gonadotropin-Releasing Hormone Analog Treatment and Cross-Sex Hormone Treatment in Adolescents With Gender Dysphoria

Daniel Klink, Martine Caris, Annemieke Heijboer, Michael van Trotsenburg, and Joost Rotteveel

Center of Expertise on Gender Dysphoria (D.K., M.v.T., J.R.); Department of Pediatrics, Division of Endocrinology (D.K., M.C., J.R.); Department of Clinical Chemistry (A.H.); and Department of Obstetrics and Gynaecology (M.v.T.), VU University Medical Center, de Boelelaan 1118 1081 HZ Amsterdam, The Netherlands

J Clin Endocrinol Metab, February 2015, 100(2):E270–E275

- 15 trans women, 19 trans men
- BMD by DXA: prior to GnRHa, at start of Cross-Sex Hormones (CSH), at 22 yrs
- Mean age 14.9-15 years, median Tanner 4-5
- GnRHa monotherapy duration: median 1.3-1.5 years
- CSH duration: median 5.4-5.8 years

Bone mass development during sex-reassignment treatment

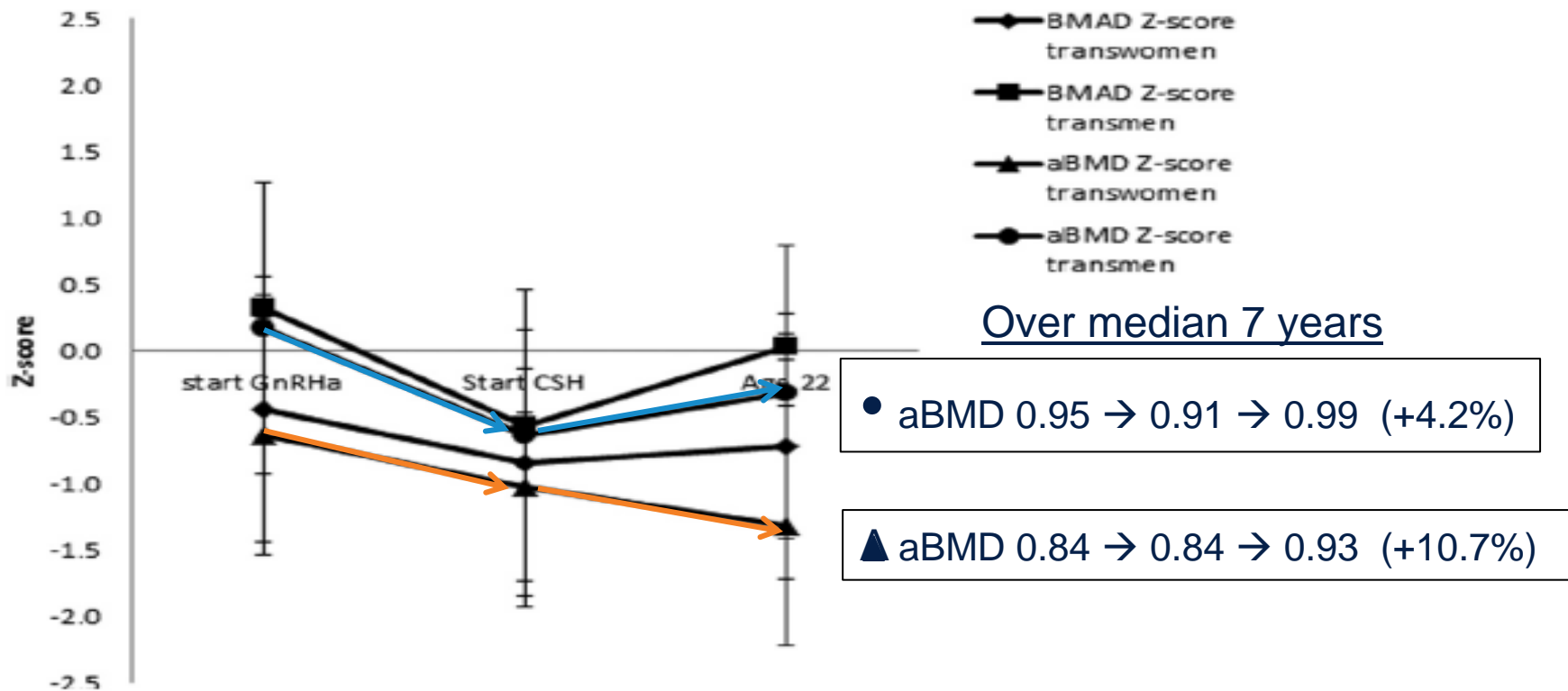


Figure 1. Longitudinal z-score (mean \pm SD) development of the LS from start medical treatment until the age of 22 years in transmen and transwomen.

Effect of pubertal suppression and cross-sex hormone therapy on bone turnover markers and bone mineral apparent density (BMAD) in transgender adolescents

Mariska C. Vlot^{a,b}, Daniel T. Klink^{c,d}, Martin den Heijer^{b,c}, Marinus A. Blankenstein^a, Joost Rotteveel^{c,d}, Annemieke C. Heijboer^{a,*}

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Bone 95 (2017) 11–19

- **42 trans men, 28 trans women**
- Median age (bone age) **15.1 yrs (15 yrs) / 13.5 yrs (13.5 yrs)**
- Median Tanner Stage **5 (2-5) / 3 (2-5)**
- BMD by DXA: prior to GnRHa, prior to CSH, 2 years after CSH
- Subdivided into young and old cohorts based on bone age
 - Transgender boys **<14 years and ≥14 years**
 - Transgender girls **<15 years and ≥15 years**
- Bone turnover markers: ± 90 days, non-fasting

Bone Turnover Markers and BMAD

D0 – prior to GnRHa, C0 – prior to CSH, C24 – 24 months after CSH

- P1NP & ICTP decreased more in the “**young**” vs. “**old**” cohorts
 - Trans men:
 - P1NP **783 → 324 → 186** vs. **110 → 127 → 101**
 - ICTP **24 → 11 → 12** vs. **7 → 6.9 → 8.2**
 - Trans women:
 - P1NP **935 → 363 → 204** vs. **191 → 140 → 119**
 - ICTP **23 → 13 → 10** vs. **12 → 7.4 → 6.8**
- LS BMAD Z-scores by DXA: lower in trans women, especially younger

Bone Development in Transgender Adolescents Treated With GnRH Analogues and Subsequent Gender-Affirming Hormones

The Journal of Clinical Endocrinology & Metabolism, 2020, Vol. 105, No. 12, 1–12

doi:10.1210/clinem/dgaa604

Clinical Research Article

Sebastian E. E. Schagen,¹ Femke M. Wouters,² Peggy T. Cohen-Kettenis,³
Louis J. Gooren,⁴ and Sabine E. Hannema⁵

- Observational prospective study (1998-2009) – some previously reported (Klink et al 2015 and Vlot et al 2017): 54 trans girls and 73 trans boys
 - GnRHa (2-4 years): 51 trans girls & 70 trans boys
 - GnRHa + hormones (3 years): 36 trans girls and 42 trans boys
- BMAD Z-scores, fasting serum bone markers (P1NP/P3NP/osteocalcin, 1CTP)
- Early-pubertal group (Tanner 2-3)
 - GnRHa: 15 trans girls and 14 trans boys
 - GnRHa + hormones: 10 trans girls and 5 trans boys
- Late-pubertal group (Tanner 4-5)
 - GnRHa: 36 trans girls and 56 trans boys
 - GnRHa + hormones: 26 trans girls and 37 trans boys

BMAD and BMAD z-scores during GnRHa

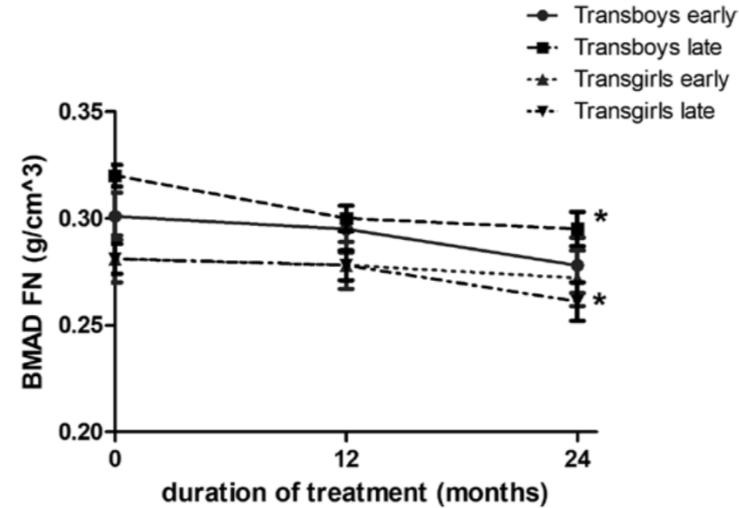
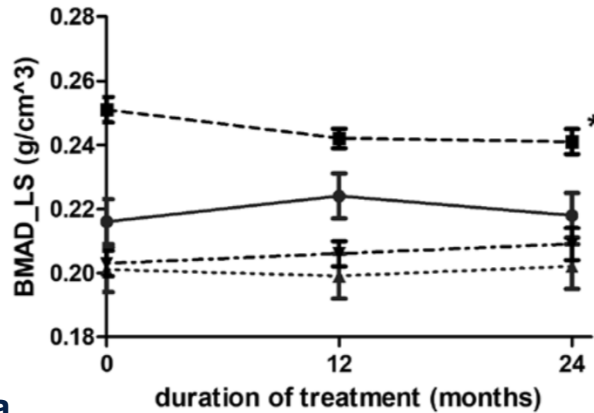
After 2 years of GnRHa

BMAD Z-scores <-2 in:

4 trans girls at hip

3 trans girls at LS

2 trans boys at hip

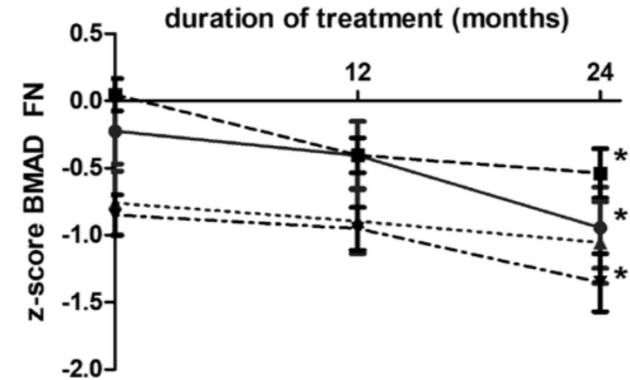
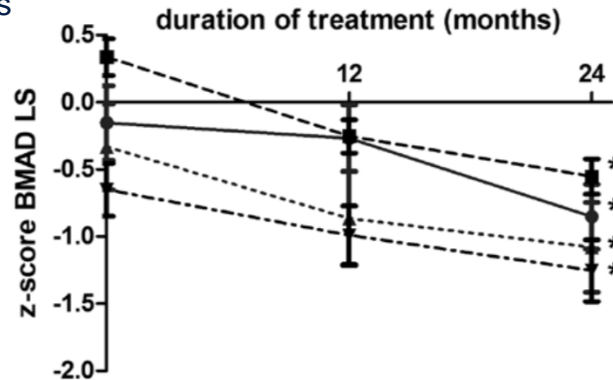


After 3 years of GnRHa

4 trans boys

11 trans girls

→ further decline in Z-scores



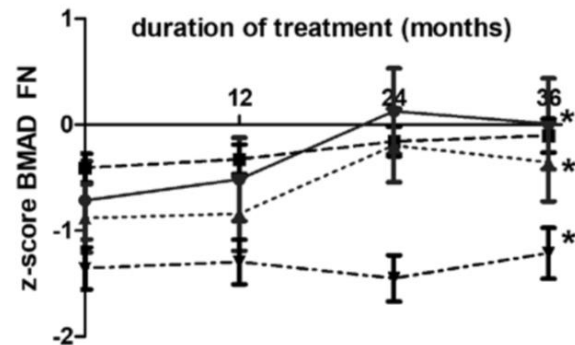
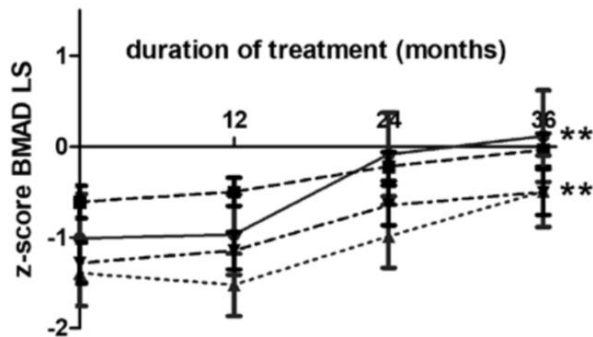
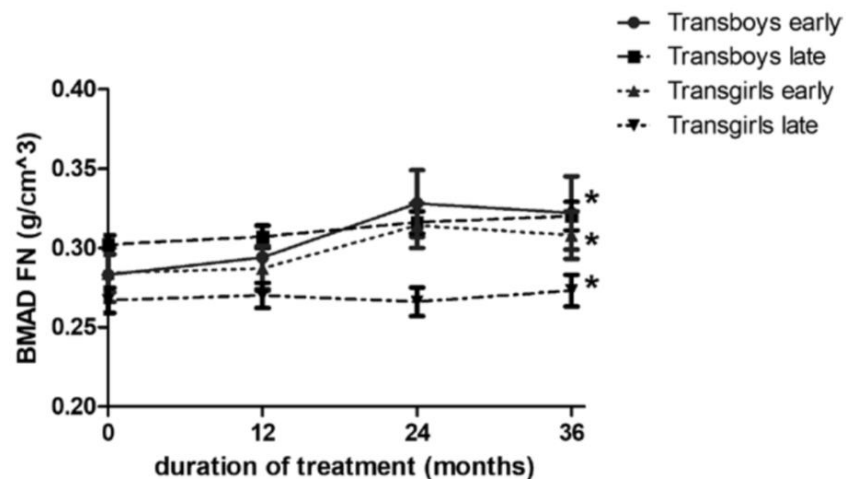
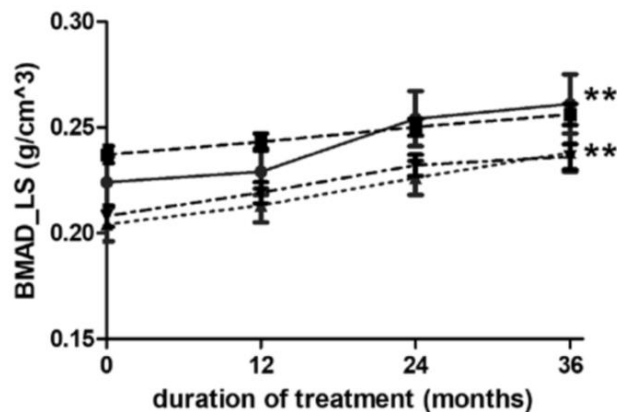
BMAD and BMAD z-scores during GnRHa and gender affirming hormones

After 3 years of GAH

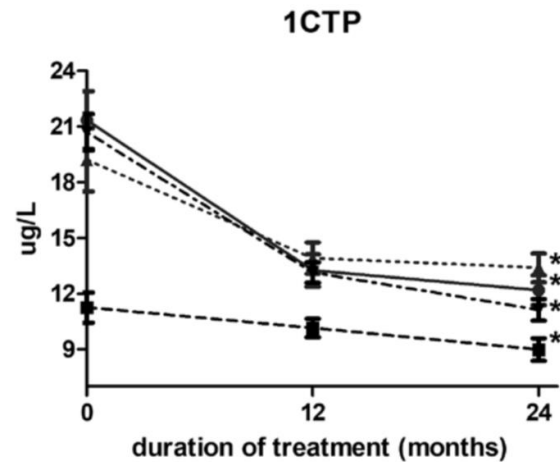
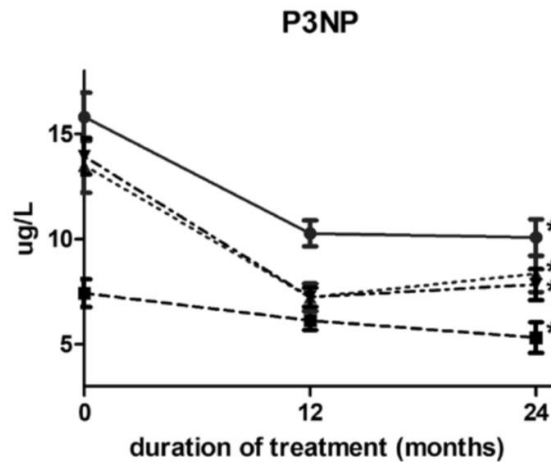
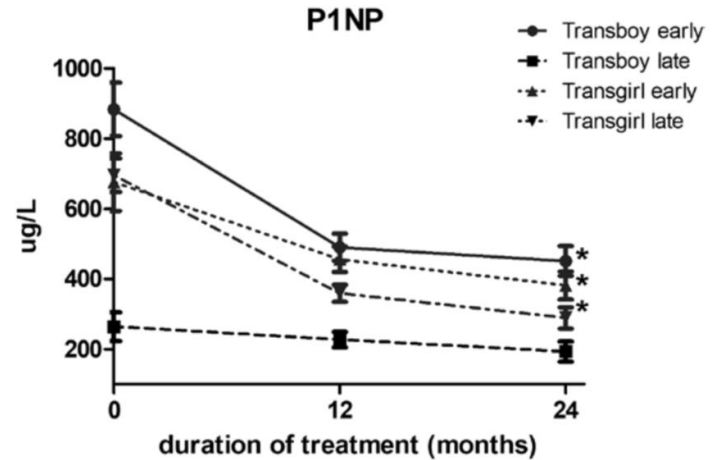
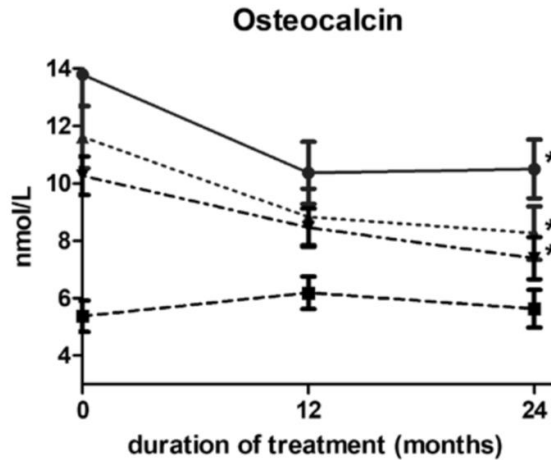
BMAD Z-scores <-2 in:

3 trans girls at hip

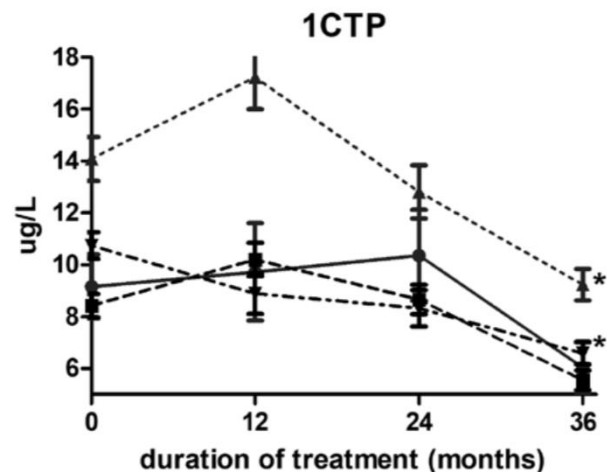
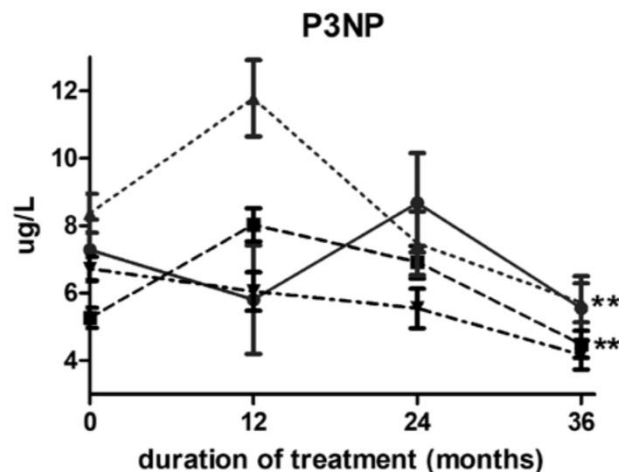
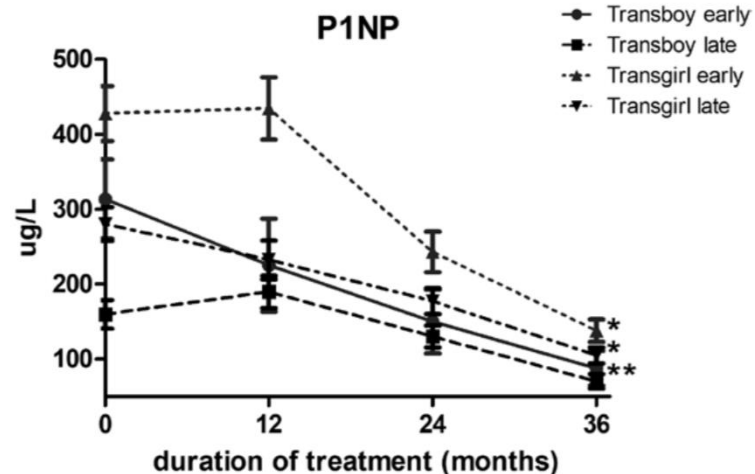
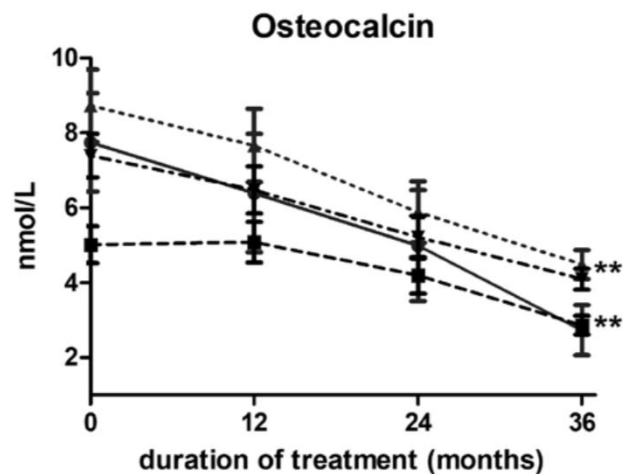
3 trans girls at LS



Serum bone markers during GnRHa treatment



Serum bone markers during GnRHa and gender affirming hormones



Original Article |  Open Access |    

Development of Hip Bone Geometry During Gender-Affirming Hormone Therapy in Transgender Adolescents Resembles That of the Experienced Gender When Pubertal Suspension Is Started in Early Puberty

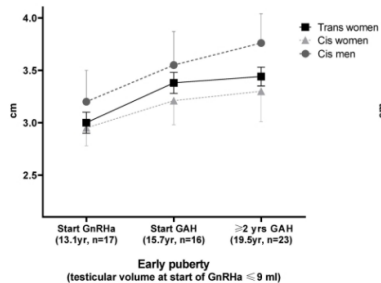
Maria ATC van der Loos, Ilse Hellinga, Mariska C Vlot, Daniel T Klink, Martin den Heijer, Chantal M Wiepjes 

First published: 28 January 2021 | <https://doi.org/10.1002/jbmr.4262>

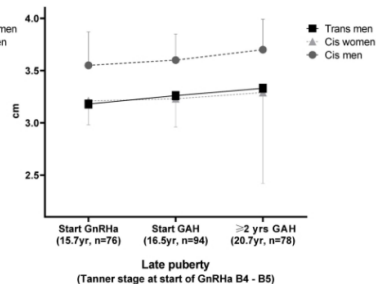
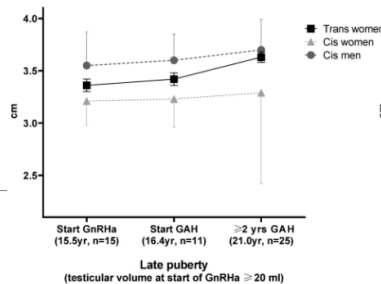
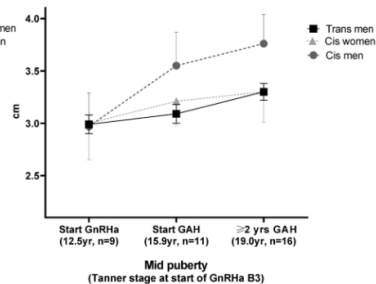
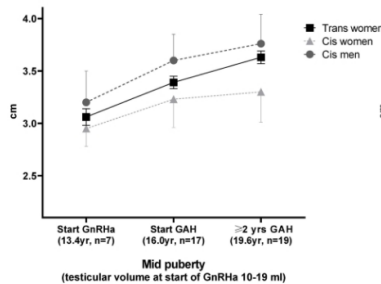
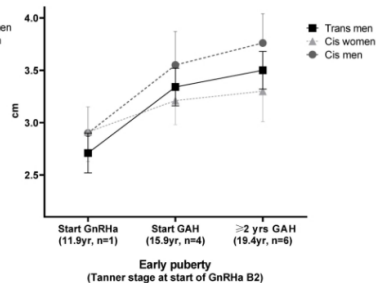
- N = 322 (**106 trans women** and **216 trans men**), pediatric treatment
- Subgroups by Tanner stage: early (**32-8**), mid (**30-22**), late puberty (**44-186**) groups
- Hip Structure Analysis software on DXA - subperiosteal width (SPW) & endocortical diameter (ED) at start of GnRHa & GAH / after ≥ 2 yrs of GAH
- Individuals who started GnRHa during early puberty resembled reference curves for SPW & ED of experienced gender

Subperiosteal width

Trans women

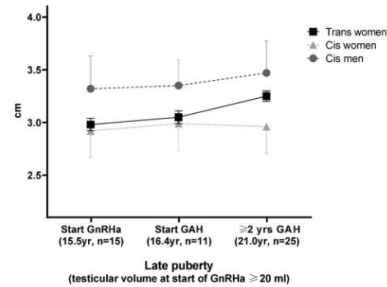
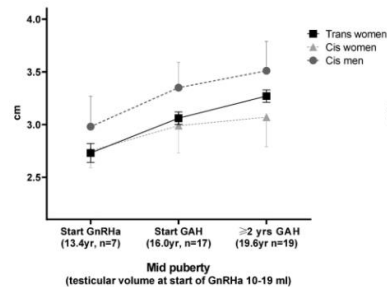
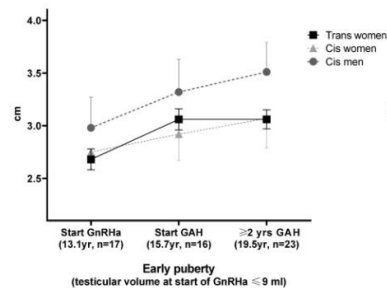


Trans men

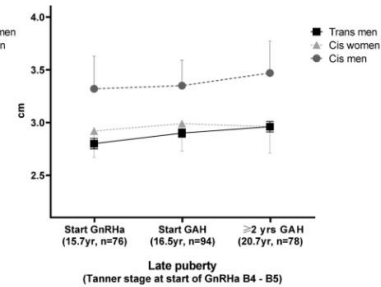
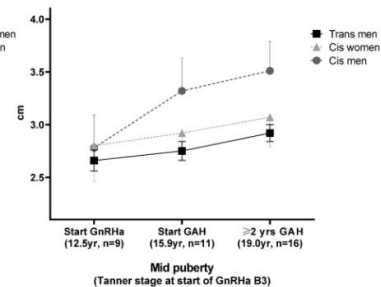
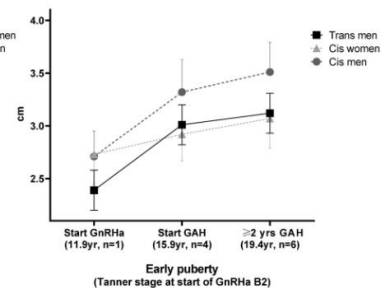


Endocortical diameter

Trans women



Trans men



Summary of Dutch Pediatric TGD Bone Data

- Transfeminine adolescent youth have lower pre-treatment BMD Z-scores (male reference ranges)
- All BMD Z-scores drop as expected on GnRHa monotherapy
- Transfeminine BMD Z-scores continue dropping in some youth despite estradiol therapy for several years
- Bone turnover markers decrease with gender-affirming medical therapy
- There may be differential effects on bone depending on pubertal stage at which gender-affirming medical therapy starts
- Bone geometry resembles references of experienced gender in TGD individuals who start GnRHa in early puberty

The Impact of Early Medical Treatment in Transgender Youth


NIH/NICHD R01, multiple PI format

- First longitudinal observational study of transgender youth funded by NIH
- Multiple sites: UCSF, CHLA, Boston Children's, Lurie Children's
- **Early Puberty Cohort (n = 95), initiating puberty blockers**
- Late Puberty Cohort (n = 301), initiating gender-affirming sex hormones, some treatment naïve and some already on blockers
- Measures: mental health, psychological well-being, metabolic and physiologic parameters, **bone health measures (DXA or QCT), vitamin D status, dietary calcium intake and physical activity assessments (PAQ-C)**

Low bone mineral density in early pubertal transgender/gender diverse youth: Findings from the Trans Youth Care Study

Journal of the Endocrine Society, bvaa065, <https://doi.org/10.1210/jendso/bvaa065>

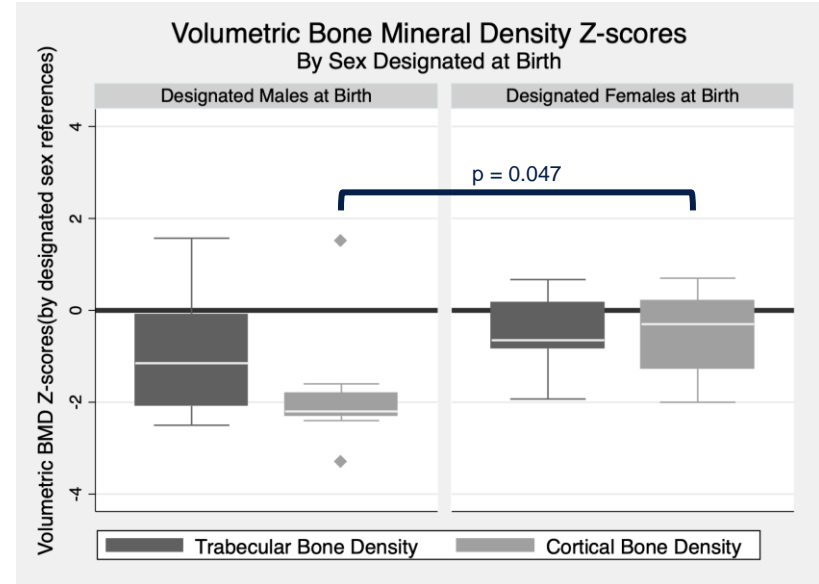
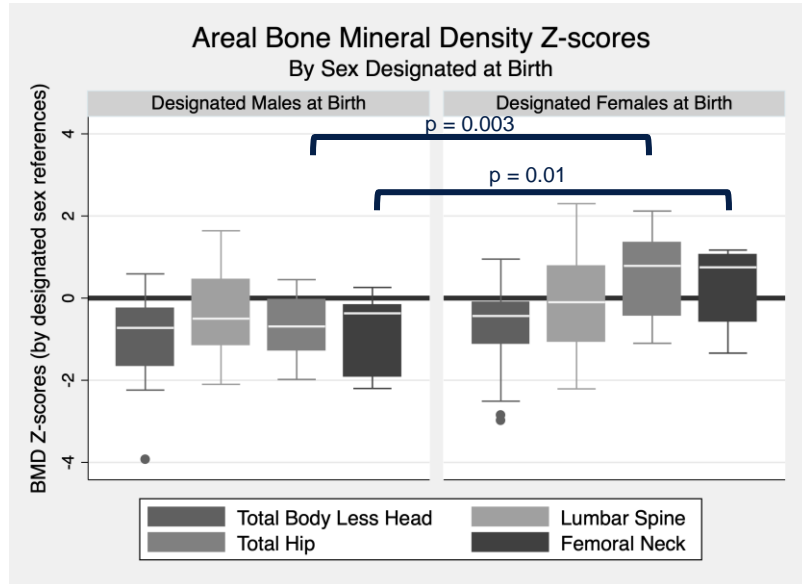
Published: 02 July 2020 Article history ▼

Janet Y Lee, MD, MPH, MAS , Courtney Finlayson, MD, Johanna Olson-Kennedy, MD, Robert Garofalo, MD, MPH, Yee-Ming Chan, MD, PhD, David V Glidden, PhD, Stephen M Rosenthal, MD

- 63 TGD youth in **Tanner Stage 2-3** (63.5% Tanner 2)
 - 33 designated males at birth (trans feminine)
 - 30 designated females at birth (trans masculine)
- DXA or QCT (hip and spine) prior to gender-affirming medical therapy, physical activity (PAQ-C: 1 = lowest activity, 5 = highest activity), dietary calcium intake, 25-OHD
- 30% designated males at birth and 13% designated females at birth had 1+ BMD Z-score <-2
- TGD youth with low BMD (n = 14) scored lower on PAQ-C, 2.32 ± 1.71 vs. 2.76 ± 0.61 (p = 0.01)
- All TGD youth had sub-optimal calcium intake ~500-600mg/day

Areal & Volumetric BMD Z-scores

By Sex Designated at Birth



Multivariate Linear Regression Models

Significant predictors of BMD Z-scores

- Predictors included: sex designated at birth, PAQ-C score, BMI Z-score, Tanner stage, age, dietary calcium intake, serum 25-OH D.
- Positive predictors for TBLH BMD Z-scores: BMI Z-scores ($p < 0.0001$)
- Positive predictors for TH BMD Z-scores: female sex ($p = 0.04$) and 25-OH D ($p = 0.048$)
- Negative predictor of TH BMD Z-score: age ($p = 0.049$)
- Negative predictor of FN BMD Z-score: age ($p = 0.02$)
- Summary:
 - higher BMI Z-scores \rightarrow higher TBLH BMD Z-scores
 - female sex and higher 25-OHD \rightarrow higher TH BMD Z-scores
 - later age \rightarrow lower hip BMD Z-scores

Summary

- We found a high prevalence of low BMD in early-pubertal TGD youth prior to GnRHa therapy, trans feminine > trans masculine
- Differences were most pronounced and significant at hip sites, reflecting potential impact of decreased physical activity
- Lower physical activity observed overall, but significantly lower in trans feminine than in trans masculine and lower in the low BMD group than in the normal BMD group
- TGD youth may not be achieving optimal dietary calcium intake
- Longitudinal data analyses forthcoming
- Coming soon!: prospective study on the skeletal effects of puberty suppression in early pubertal TGD youth over one year, utilizing DXA and HR-pQCT (n = 30)

Approach to Transgender/Gender Diverse Youth

During Suppression of Puberty

- Endocrine Society Suggestions (baseline & every 1-2 years):
 - Bone age radiograph to assess growth
 - Bone density using DXA
- **“BMD should be monitored into adulthood (until the age of 25-30 y or until peak bone mass has been reached).”**
- No specific bone-related recommendations for TGD youth initiating gender-affirming medical therapy in late adolescence
- My own suggestions: Consider baseline DXA in all TGD youth (maybe even pre-puberty) who have risk factors for low BMD (eating disorders, low BMI, low physical activity, etc)

Bone Density in Transgender Women

When compared with cisgender men reference data

- Prior to treatment:
 - Lower aBMD at spine, total hip, and femoral neck
 - Van Caenegem E et al; Figuera TM et al
- On gender-affirming estrogen therapy:
 - Stable to increased aBMD
 - Sing-Ospina N et al; Van Caenegem E et al; Mueller A et al; Dittrich R et al; Reutrakul S et al; Wiepjes CM et al

Bone Density in Transgender Men

When compared with cisgender women reference data

- Overall – more favorable BMD measurements
- Prior to treatment:
 - Similar aBMD at spine, total hip, and femoral neck
 - Van Caenegem E et al; Haraldsen IR et al
- On gender-affirming testosterone therapy:
 - Stable to increased aBMD
 - Sing-Ospina N et al; Van Caenegem E et al; Figuera et al; Wiepjes CM et al; Turner et al; Mueller et al; Pelusi et al

Fracture Risk in Trans Women and Trans Men Using Long-Term Gender-Affirming Hormonal Treatment: A Nationwide Cohort Study

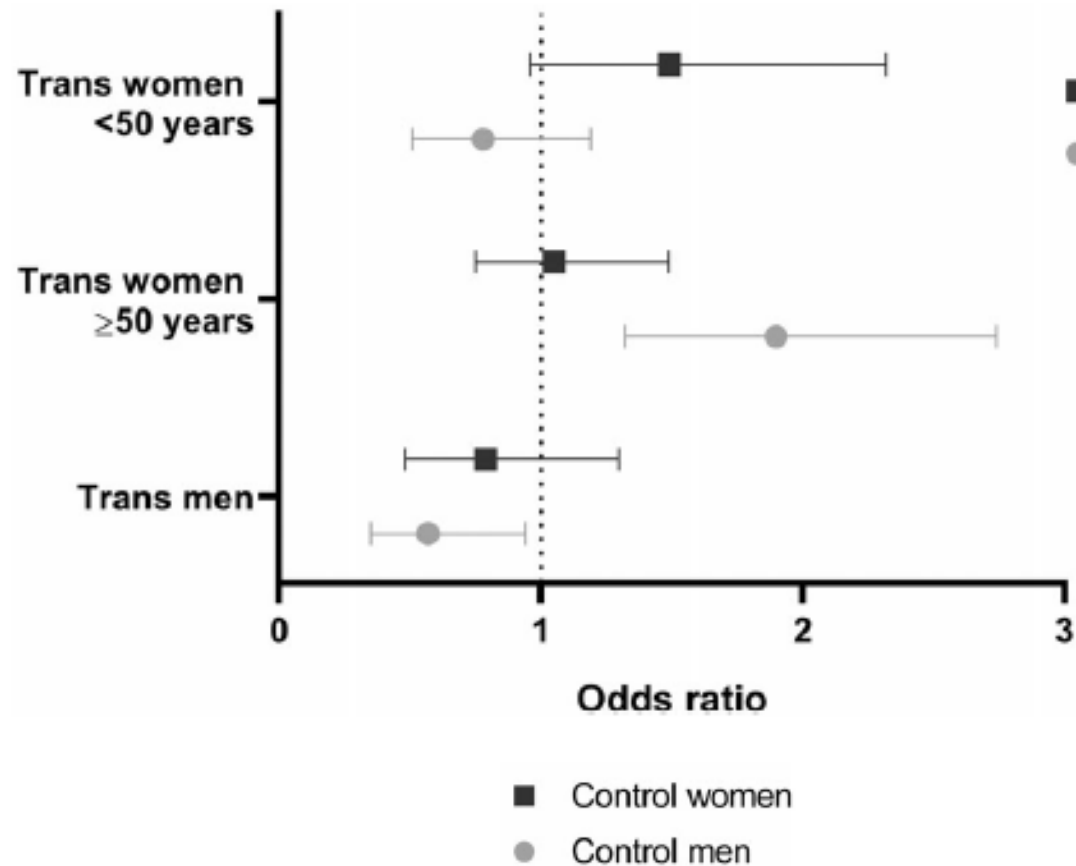
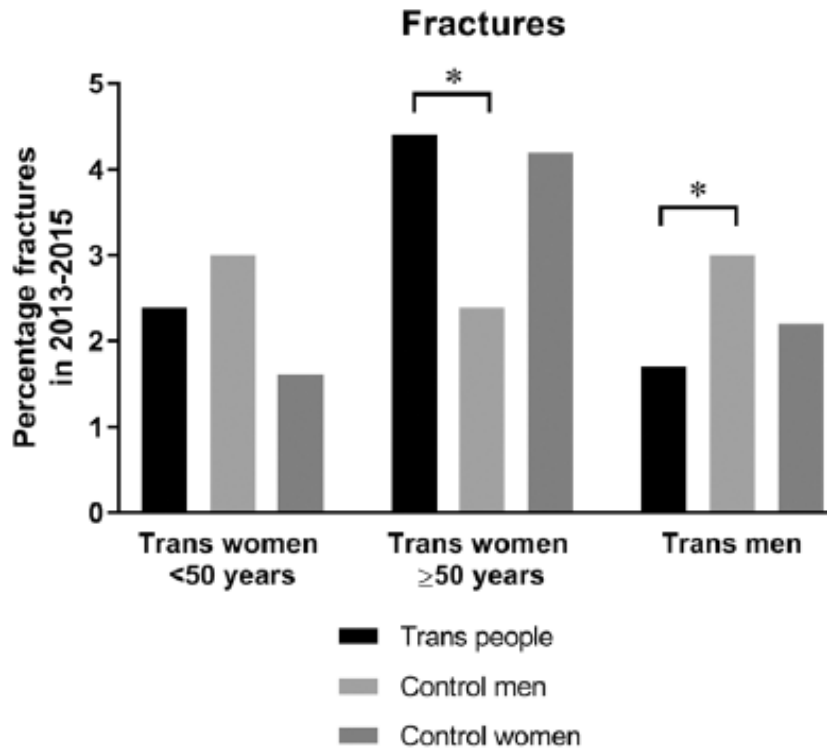
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- **1089 trans women <50 yrs (38 ± 9 yrs)** and **934 trans women ≥ 50 yrs (60 ± 8 yrs)**
- **1036 trans men (40 ± 14 yrs)**
- Median **8 yrs** and **19 yrs** of estrogen, **9 yrs** of testosterone
- Median age at start of hormone therapy: **26 yrs**, **40 yrs**, **25 yrs**
- 5 age-matched reference men and 5 age-matched reference women
- Fracture data: medical visits 2013-2015



Summary

- Transfeminine individuals of all ages tend to have lower BMD Z-scores prior to treatment (when compared to sex designated at birth)
- In transfeminine youth, lower physical activity may contribute to low BMD Z-scores
- TGD youth may have sub-optimal dietary calcium intake
- TGD youth may not return to baseline BMD Z-scores after several years of gender-affirming sex hormones
- Fracture risk may be higher in older trans women compared with cis men (and in younger trans women compared with cis women)

Approach to Transgender/Gender Diverse Adult

Endocrine Society Clinical Practice Guidelines (2017)

- Transgender Male:

- Screening for osteoporosis should be conducted in those who have had gonadectomy and stop testosterone treatment, are not compliant with hormone therapy, or develop risks for bone loss.

- Transgender Female:

- Consider BMD testing at baseline. In individuals at low risk, screening for osteoporosis should be conducted at age 60 years or in those who are not compliant with hormone therapy (and have had gonadectomy or are on blocker therapy).

When to order DXA: TGD Individuals

International Society for Clinical Densitometry (ISCD) 2019 Official Position

- Baseline BMD if:
 - Gonadectomy or endogenous sex steroid-lowering treatment before gender-affirming hormone therapy
 - Hypogonadism without gender-affirming hormone therapy
- Follow BMD if:
 - Results will influence patient management (low BMD, individuals on GnRHa, non-adherence to hormones, other risk factors)
 - Testing intervals individualized, every 1-2 yrs until stable/improved

Interpretation of DXA: TGD Individuals

International Society for Clinical Densitometry (ISCD) 2019 Official Position

- T- and Z-score calculations
 - T-scores: Caucasian female normative database for all TGD individuals regardless of ethnicity
 - Z-scores: Use normative database matching gender identity, but may also request normative database matching sex designated at birth
- Non-binary individuals:
 - Normative database that matches sex designated at birth
- Osteoporosis: T-score ≤ -2.5 in TGD individuals ≥ 50 years old

Bone Densitometry in Transgender and Gender Nonconforming (TGNC) Individuals: The 2019 ISCD Official Positions

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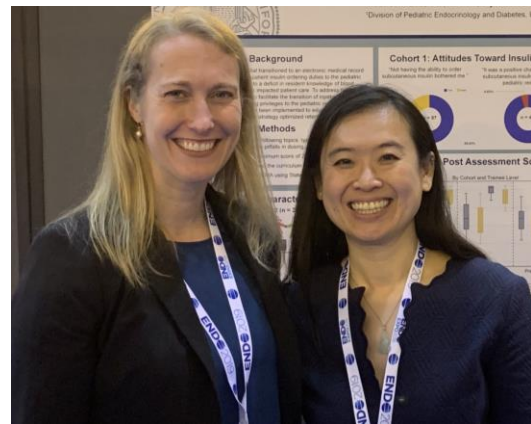
Future Directions

Answers still needed!

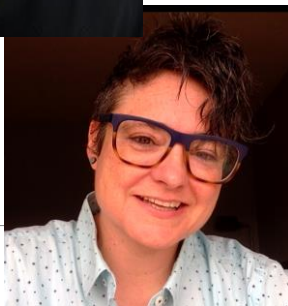
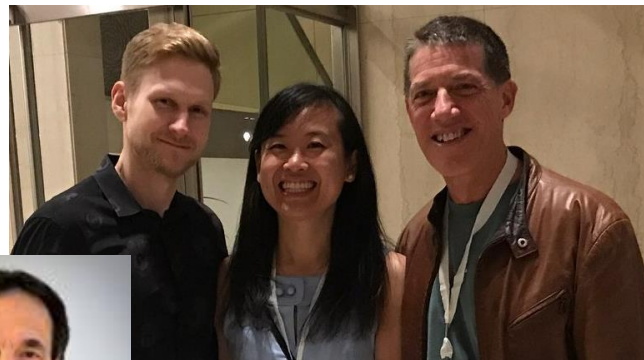
- Which reference standards should we be using for DXA?
- When is peak bone mass achieved in TGD youth who initiate gender-affirming medical therapy in early puberty (and is it less than expected)?
- What is the fracture risk in TGD individuals who initiate gender-affirming medical therapy in early puberty?
- How could we time initiation of gender-affirming sex hormones to optimize bone mass?
- What strategies can be used to mitigate low BMD if discovered in TGD youth and young adults?
- How should we assess and interpret BMD in non-binary individuals?

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Thanks!



Thank You

Questions?

