Transgender Medicine and Bone Health

2021 Interdisciplinary Symposium on Osteoporosis (ISO2021)

Janet Y. Lee, MD, MPH, MAS
Assistant Professor of Pediatrics and of Medicine
Divisions of Pediatric Endocrinology & Endocrinology and Metabolism
University of California, San Francisco

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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

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


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

- Approximately 150,000 youth in the United States
- Approximately 1.4 million adults in the United States

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>13 to 17</td>
<td>0.7%</td>
</tr>
<tr>
<td>18 to 24</td>
<td>0.7%</td>
</tr>
<tr>
<td>25 to 64</td>
<td>0.6%</td>
</tr>
<tr>
<td>65 and older</td>
<td>0.5%</td>
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<tr>
<td>All Adults (18+)</td>
<td>0.6%</td>
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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

<table>
<thead>
<tr>
<th>Early Childhood</th>
<th>Late Childhood/Pre-Puberty</th>
<th>Early Puberty</th>
<th>Late Puberty</th>
<th>Adulthood</th>
</tr>
</thead>
<tbody>
<tr>
<td>School Resources, Social Transition</td>
<td>Puberty Blockers: GnRH agonists</td>
<td>Gender-Affirming Sex Hormones</td>
<td>Surgeries</td>
<td>Fertility Preservation</td>
</tr>
</tbody>
</table>
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)

DNA NAR 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

Over median 7 years

- aBMD $0.95 \rightarrow 0.91 \rightarrow 0.99$ ($+4.2\%$)

- aBMD $0.84 \rightarrow 0.84 \rightarrow 0.93$ ($+10.7\%$)

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

Osteocalcin

P1NP

P3NP

1CTP

Transboy early
Transboy late
Transgirl early
Transgirl late
Serum bone markers during GnRHa and gender affirming hormones

**Osteocalcin**

- Transboy early
- Transboy late
- Transgirl early
- Transgirl late

**P1NP**

**P3NP**

**1CTP**

(duration of treatment (months))

(duration of treatment (months))

(duration of treatment (months))

(duration of treatment (months))
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
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

Janet Y Lee, MD, MPH, MAS 2, 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

Areal Bone Mineral Density Z-scores
By Sex Designated at Birth

<table>
<thead>
<tr>
<th></th>
<th>Designated Males at Birth</th>
<th>Designated Females at Birth</th>
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<tbody>
<tr>
<td></td>
<td>p = 0.003</td>
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<tr>
<td></td>
<td>p = 0.01</td>
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Volumetric Bone Mineral Density Z-scores
By Sex Designated at Birth

<table>
<thead>
<tr>
<th></th>
<th>Designated Males at Birth</th>
<th>Designated Females at Birth</th>
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<tbody>
<tr>
<td></td>
<td>p = 0.047</td>
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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 → higher TBLH BMD Z-scores
- female sex and higher 25-OHD → higher TH BMD Z-scores
- later age → 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; Fighera 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; Fighera 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

Chantal M Wiepjes,1,2 Christel JM de Blok,1,2 Annemieke S Staphorsius,2 Nienke M Nota,1,2 Mariska C Vlot,1,2 Renate T de Jongh,1 and Martin den Heijer1,2

1Department of Endocrinology, Amsterdam UMC, VU University Medical Center, Amsterdam, the Netherlands
2Center of Expertise on Gender Dysphoria, Amsterdam UMC, VU University Medical Center, Amsterdam, the Netherlands

- 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

Harold N. Rosen,1,* Ole-Petter R. Hamnvik,2 Unnop Jaisamrarn,3
Alan O. Malabanan,1 Joshua D. Safer,4 Vin Tangpricha,5,6
Lalita Wattanachanya,7,8 and Swan S. Yeap9

1 Division of Endocrinology and Metabolism, Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA, USA; 2 Division of Endocrinology, Diabetes and Hypertension, Department of Medicine, Brigham and Women’s Hospital, Boston, MA, USA; 3 Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand; 4 Mount Sinai Health System, Icahn School of Medicine at Mount Sinai, Center for Transgender Medicine and Surgery, New York, NY, USA; 5 Division of Endocrinology, Metabolism & Lipids, Department of Medicine, Emory University School of Medicine, Atlanta, GA, USA; 6 Atlanta VA Medical Center, Decatur, GA, USA; 7 Division of Endocrinology and Metabolism, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand; 8 Excellence Center for Diabetes, Hormone, and Metabolism, King Chulalongkorn Memorial Hospital, Bangkok, Thailand; and 9 Department of Medicine, Subang Jaya Medical Centre, Subang Jaya, Selangor, Malaysia

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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?
With Much Gratitude to:

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  - Stephen Rosenthal, MD
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  - Jenise Wong, MD, PhD
  - Ellen Fung, RD, PhD
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  - Dolores Shoback, MD
  - Edward Hsiao, MD, PhD
  - Roger Long, MD
  - Srinath Sanda, MD

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  - Stanley Vance, MD
  - Diane Ehrensaft, PhD
  - Erica Anderson, PhD
  - Jessie Cohen, LCSW
  - Julia Baghai, RN, MSN

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  - Dennis Black, PhD
  - David Glidden, PhD
  - Bo Fan, MD
  - Thomas Link, MD, PhD

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  - UCSF CCMBM Voucher Program Award
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Thanks!
Thank You

Questions?