MAYO CLINIC | School of Continuous Professional Development

BONE HEALTH IN TRANSGENDER PEOPLE

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DISCLOSURE OF RELEVANT FINANCIAL RELATIONSHIP(S) WITH INELIGIBLE COMPANIES

- Nothing to disclose
- USPATH Board of Directors

REFERENCES TO OFF-LABEL USAGE(S) OF PHARMACEUTICALS OR INSTRUMENTS

- Hormone therapy for gender dysphoria/incongruence off label

All relevant financial relationships have been mitigated.

LEARNING OBJECTIVES

- Review specific skeletal considerations in transgender and gender diverse (TGD) people
- Discuss anticipated bone changes associated with initiation of gender-affirming hormone therapy
- Review indications for assessing bone density in TGD people, and how to interpret these studies

TERMINOLOGY

- **Transgender**: Sex designated at birth and gender identity are incongruent
  - Transgender woman: designated male at birth, identifies as female/feminine
- **Cisgender**: Sex designated at birth and gender identity are congruent
- **Gender nonbinary**: identify as neither male nor female, both male and female or along/outside the gender spectrum
- **Gender dysphoria**: clinical distress associated with incongruency between sex designated at birth and gender identity

QUESTION 1

- A 36-year-old transgender woman presents to your office to initiate hormone therapy for gender dysphoria/incongruence. She is generally healthy and does not take any medications. She smoked a pack of cigarettes per day for 5 years but quit 2 years ago. Baseline laboratory tests are normal, including testosterone level. What would be your next step in evaluation of skeletal health?
- Check a baseline bone mineral density scan
- Ask about calcium and vitamin D intake
- No additional skeletal-focused evaluation is needed because hormone therapy will improve bone density even if low at baseline
- Check parathyroid hormone level

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Van Caenegem et al Osteop Int 2016

RATIONALE

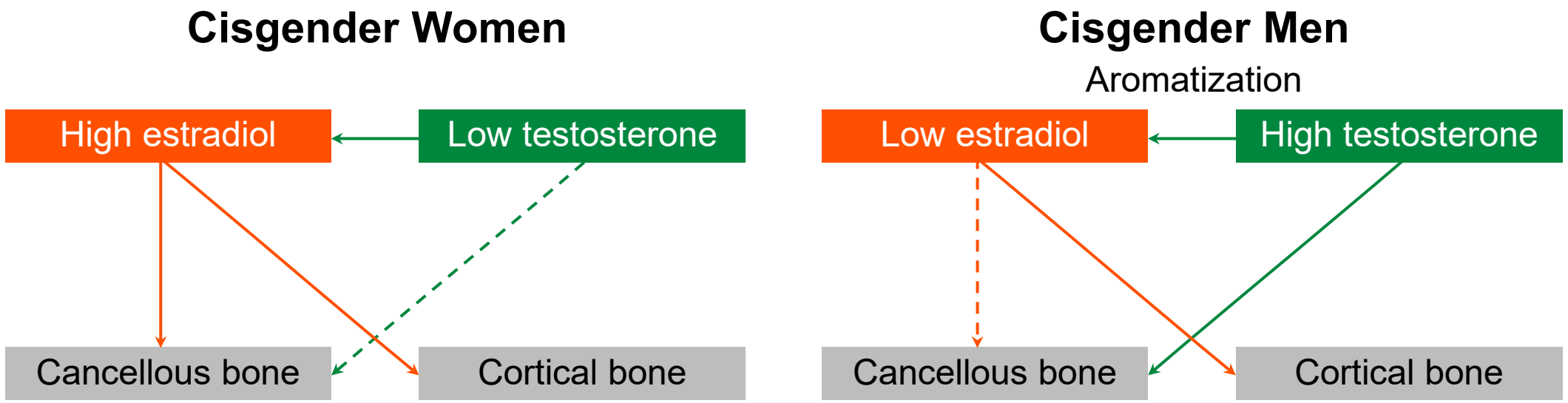
Vitamin D deficiency is common in transgender women, and this likely exacerbates low baseline bone mineral density. Therefore, calcium and vitamin D intake should be discussed at clinical visits and be replaced if necessary. This patient does not have other risk factors for low bone density and so a baseline BMD DXA is not needed. Although BMD is likely to improve with estradiol therapy, those who are calcium and vitamin D deficient could have less of an improvement than those who are replete. The history of calcium and vitamin D intake would be more helpful than checking a parathyroid hormone level.

- Reference

Van Caenegem et al Osteop Int 2016

EFFECTS OF SEX STEROIDS ON BONE

- During puberty - bone density, width and length increase

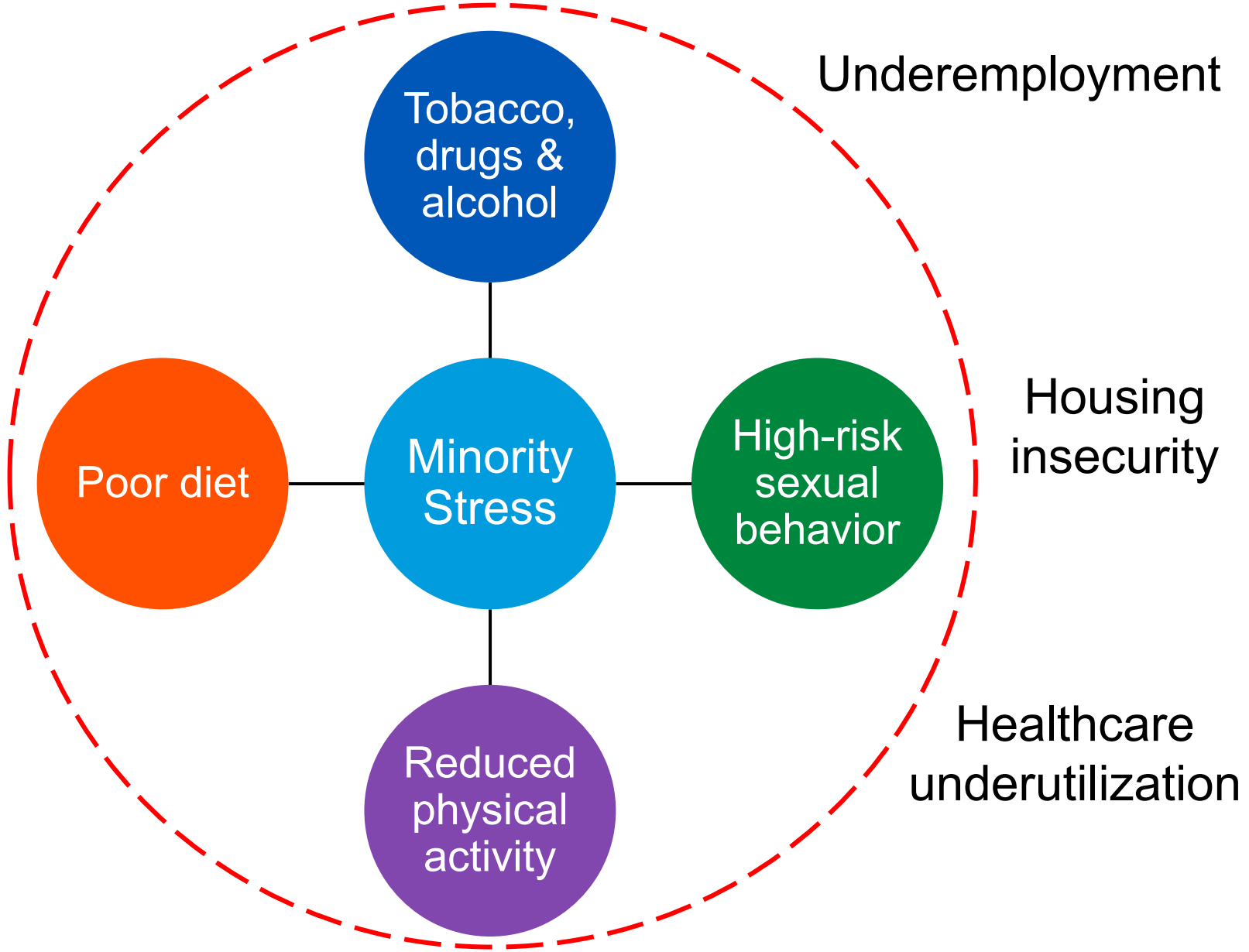


Davidge-Pitts, Khosla Lancet Diab Endocrinol 2019

SKELETAL CONSIDERATIONS IN TRANSGENDER AND GENDER DIVERSE (TGD) INDIVIDUALS

- Age
- History of gonadectomy
- Medication considerations
  - GnRH agonists
  - Low dose hormone therapy
  - Glucocorticoids
- Body Composition
- Established risk factors for adverse skeletal health

Minority stress can increase risk for poorer coping & health behaviors



Redrawn from Image created by Tyson Pankey

BONE HEALTH PRIOR TO HORMONE THERAPY: TRANSFEMININE PEOPLE

Compared to cisgender men

- Significantly lower mean areal BMD at spine (8.5%), hip (13%) and femoral neck (14.3%)
- Radial and tibial cortical bone area were smaller
- Significantly lower serum 25(OH)D and higher PTH
- Significantly lower body lean mass, lower grip strength and muscle mass
- Lower weekly sport activity

Osteoporos Int (2015) 26:35–47
DOI 10.1007/s00198-014-2805-3

ORIGINAL ARTICLE

Preservation of volumetric bone density and geometry in trans women during cross-sex hormonal therapy: a prospective observational study

E. Van Caenegem · K. Wierckx · Y. Taes · T. Schreiner · S. Vandewalle · K. Toye · J.-M. Kaufman · G. T'Sjoen

49 trans women before hormone therapy
Median age 30 years

BONE HEALTH PRIOR TO HORMONE THERAPY: TRANSMASCULINE PEOPLE

Compared to cisgender women

- Similar areal BMD, trabecular, and cortical vBMD, cortical bone size
- Similar bone turnover markers
- Higher rate of smoking (26% vs 9%)
- Similar fat, muscle mass and strength

Clinical Study | E Van Caenegem and others | Bone metabolism in trans men | 172:2 | 163–171

Body composition, bone turnover, and bone mass in trans men during testosterone treatment: 1-year follow-up data from a prospective case–controlled study (ENIGI)

E Van Caenegem[1,2], K Wierckx[1,2], Y Taes[1], T Schreiner[2,3], S Vandewalle[1], K Toye[1], B Lapauw[1], J-M Kaufman[1] and G T'Sjoen[1,2,4]

[1]Department of Endocrinology, Ghent University Hospital, De Pintelaan 185, 9000 Ghent, Belgium, [2]European Network for the Investigation of Gender Incongruence (ENIGI), Ghent, Belgium, [3]Department of Endocrinology, Rikshospitalet, Oslo University Hospital, Sognsvannvn 20, Oslo, Norway and [4]Center for Sexology and Gender Problems, Ghent University Hospital, De Pintelaan 185, Ghent, Belgium

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23 trans men before hormone therapy

HORMONE THERAPY FOR TRANSFEMININE PEOPLE

Anti-androgen

- Spironolactone 100-200 mg per day
- Cyproterone acetate 10 mg per day (not in US)
- Other: GnRH agonists, finasteride, bicalutamide

Estradiol

- Oral: estradiol 2 - 8 mg per day
- IM/SC 2 – 8 mg per week
- Patches 0.025 – 0.3 mg/day
- Gels

Do not recommend conjugated equine estrogens or ethinyl estradiol

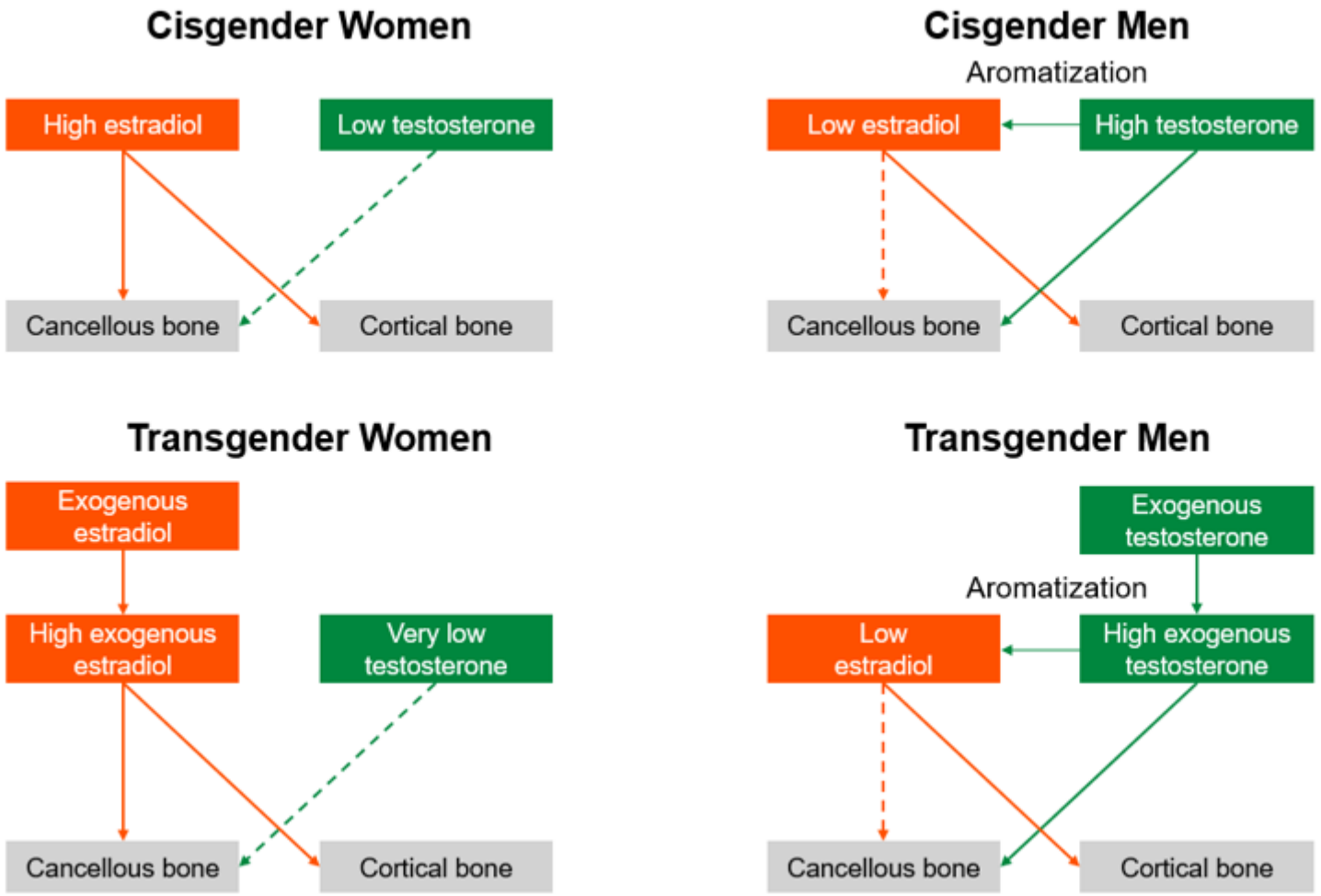
Adapted from: Hembree et al J Clin Endocrinol Metab, November 2017

HORMONE THERAPY FOR TRANSMASCULINE PEOPLE

Testosterone Preparations	Route	Frequency	Self-administered?	Comments
T enanthate, T cypionate	IM or SQ	q week or q 2 weeks	Yes	Peaks & troughs Easy to titrate
T undecanoate	IM	q 10 weeks	No	Micro emboli
T enanthate	SQ autoinjector	Weekly	Yes	50 mg/0.5 mL 75 mg/0.5 mL 100 mg/0.5 mL
T gels	Topical	Daily	Yes	Trunk, thigh, axilla ? transfer to others
T patch	Topical	Daily	Yes	Rash, falls off
T undecanoate	Oral tablet	BID	Yes	Compliance, expense
T pellets	SQ	q 3 to 4 months	No	Placed with Trocar

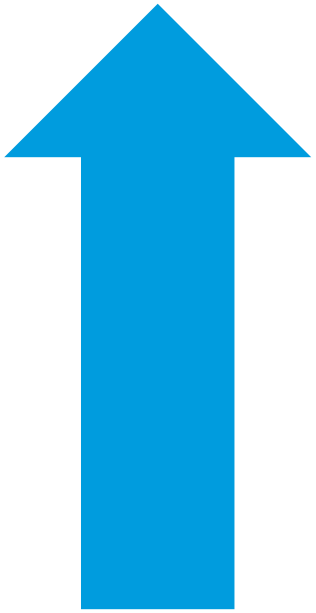
Adapted from Hembree et al J Clin Endocrinol Metab, November 2017

ANTICIPATED EFFECTS OF GENDER-AFFIRMING HORMONE THERAPY ON BONE

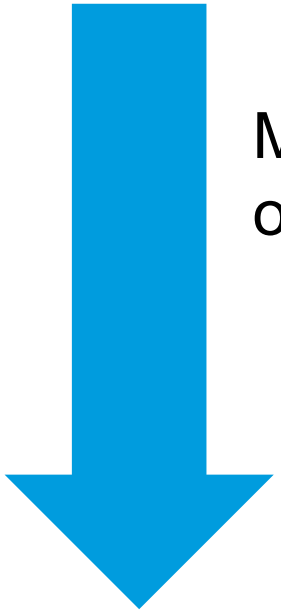


Davidge-Pitts, Khosla Lancet Diab Endocrinol 2019

ASSOCIATION BETWEEN SERUM ESTRADIOL AND SPINE BMD: TRANSFEMININE PEOPLE



Mean estradiol
121 pg/mL or 443 pmol/L



Mean estradiol 32 pg/mL
or 118 pmol/L

Bone microarchitecture (tibia, radius): 40 TW ≥1 year lower total vBMD, lower cortical vBMD, higher cortical porosity and reduced trabecular bone volume fraction relative to *cis male* controls

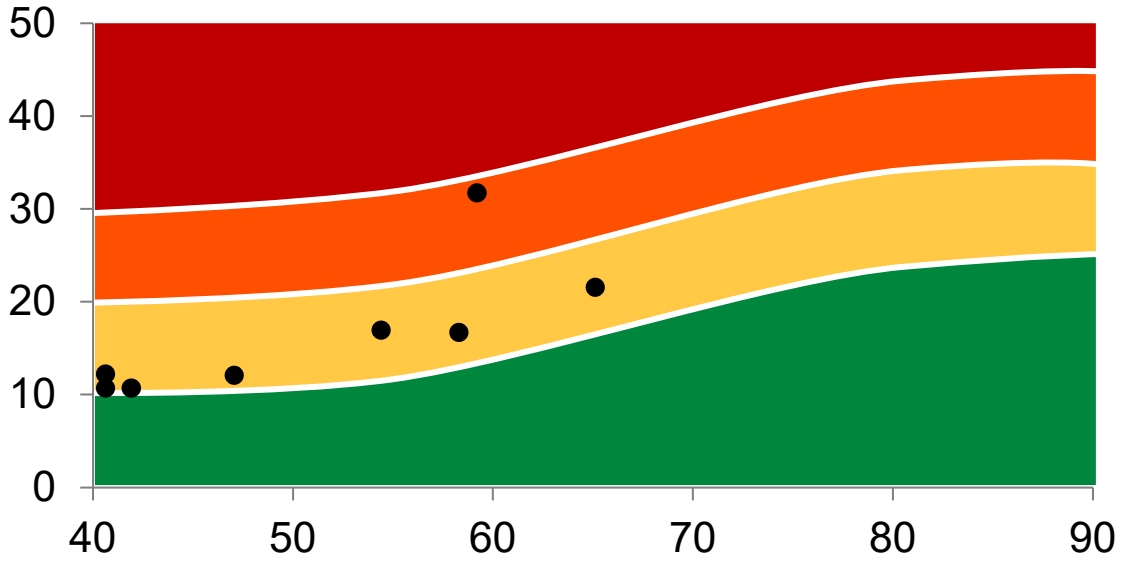
Wiepjes et al J Bone Miner Res 2018
Bretherton et al J Bone Miner Res 2022

AFTER INITIATION OF HORMONE THERAPY: TRANSMASCULINE PEOPLE

- After 1 year of GAHT, a study of 199 TM (median age 24) showed significant increases in the total hip BMD (+ 1.04%), LS (+ 0.86%)
  - LS BMD changes most pronounced in TM over age 50 years (+ 4.32%) compared to younger trans men (+0. 68%)
- After 10 years of GAHT (70 TM), LS Z-score increased by + 0.34 but in older age group (≥40 yrs) + 0.054 in LS BMD
- **Bone microarchitecture**: 41 TM ≥1 year showed higher cortical and trabecular thickness, and higher cross-sectional area and vBMD compared to cis female controls

Wiepjes et al J Bone Miner Res 2017; Vlot et al JBMR 2019; Wiepjes et al J Bone Miner Res 2018; Bretherton et al J Bone Miner Res 2022

10 YEAR FRACTURE RISK ASSESSMENT

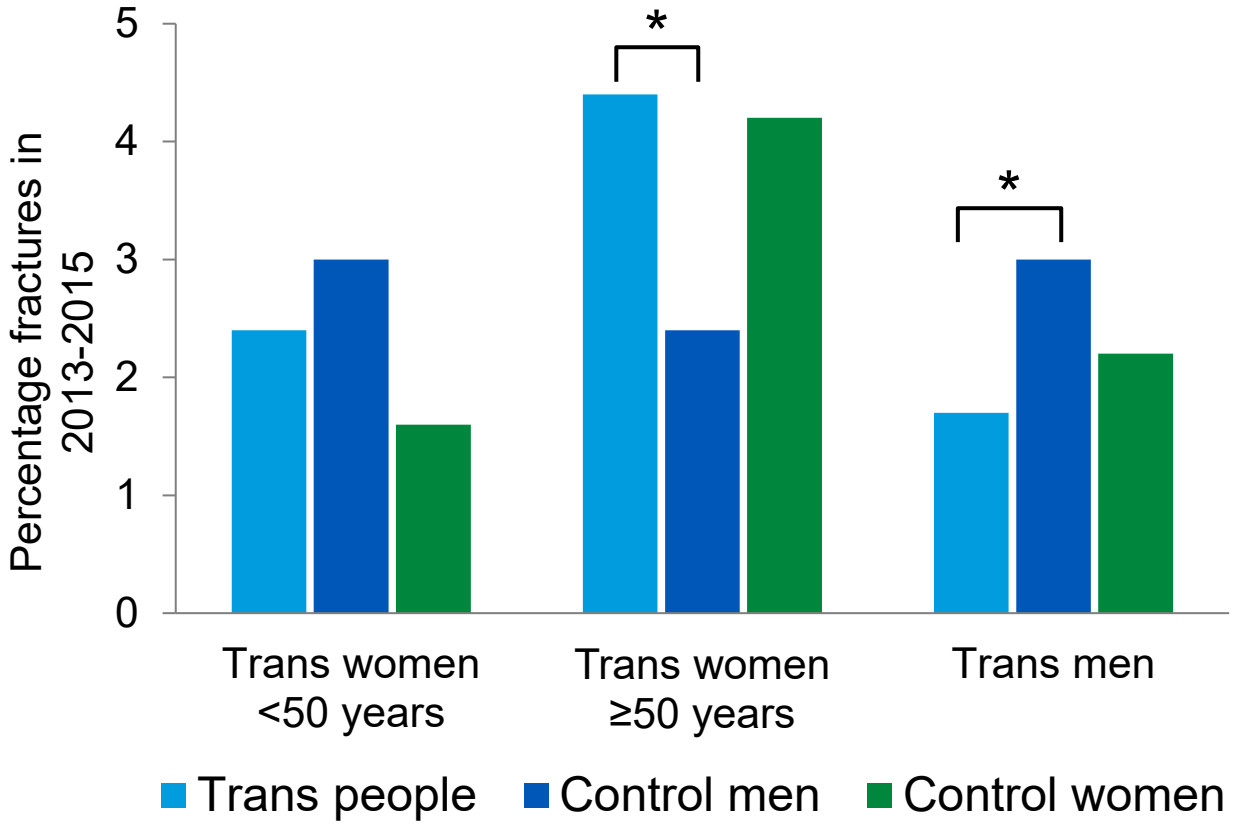


14% intermediate-high risk

- 57 TW with previous gonadectomy
- Mean age of 45.3±11.3 years
- 56% sedentary life, 37% current smokers, 93% hypovitaminosis D (<30 ng/mL)
- 51% reported low compliance with GAHT
- Low bone mass in 40% (older, lower estradiol levels, lower compliance)
- No fragility fractures

Redrawn from Motta et al J Bone and Mineral Metabolism 2020
https://defra -osteoporosi.it

FRACTURE RISK



Fracture incidence determined by visits to hospital emergency department

- 2023 trans women
  - 1089 <50yrs 934 ≥50yrs
- 1036 trans men
- TW ≥50yrs similar fractures to cis women ≥50yrs
  - Age, T score of lumbar spine, smoking → higher risk of fracture
- TM lower fractures compared to cis men

Redrawn from Wiepjes et al JBMR 2019

QUESTION 2

When interpreting BMD results in a 40-year-old transgender woman without gonadectomy, which reference range should be used for the z-score?

A. Sex recorded at birth

B. Gender identity

C. I don’t know

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B. Gender identity

C. I don't know

International Society for Clinical Densitometry guidelines 2019

RATIONALE

ISCD guidelines published in 2019 discuss the rationale of whether sex designated at birth or gender identity should be used in interpretation of BMD DXA scans in transgender and gender diverse people. For individuals age 50 and older, calculation of T scores should use the uniform caucasian female normative database, as done with cisgender people. For those under the age of 50 years, the z score calculation should use the normative database that matches gender identity. This is because data reveals that in transgender women, mean BMD at hip and spine is in fact closer to cisgender women than cisgender men. This is less clear in transgender men, where mean BMD is as at least as close to BMD in cisgender women as in cisgender men, and therefore the affirmed gender should be used. For nonbinary individuals on low dose or no hormone therapy, sex designated at birth should be used to calculate Z scores.

Reference

- International Society for Clinical Densitometry guidelines 2019

CLINICAL APPLICATION

WHEN IS BMD RECOMMENDED?

Baseline low bone density

GnRH analog therapy (Puberty suppression)

Low dose hormone therapy or nonadherence

Risk factors for bone loss

1-2 years

International Society for Clinical Densitometry guidelines 2019

T AND Z SCORES

T scores

- Uniform Caucasian female normative database
- ≥50 years

Z scores

- Normative database that matches gender identity
  - TW: BMD closer to cisgender women (hip and spine)
  - TM: Less definitive, at least as close to cisgender men and women
- Nonbinary people: Sex recorded at birth

International Society for Clinical Densitometry guidelines 2019; Fighera et al Clin Endocrinol (Oxf) 2018; Wiepjes et al J Bone Miner Res 2019; Broulik et al Horm Met Res 2018; Haraldsen et al Horm Behav 2007; Ruetsche et al Osteoporos Int 2005

THERE IS MORE WORK TO BE DONE…

- Database of TGD individuals so that appropriate Z scores can be used
- Bone microarchitecture
- Fracture risk assessment
- Recommendations for nonbinary individuals

SUMMARY

- Gender-affirming hormone therapy aligns secondary sex characteristics with affirmed gender
- Multiple studies have shown that transgender women have low baseline BMD prior to hormone therapy
- Hormone therapy, in general, seems to have positive effects on bone health in both transgender men and women. However, bone microarchitecture and fracture risk require further study
- BMD is recommended when risk factors for bone loss are present. When interpreting Z scores, it is recommended to use affirmed gender unless the person is nonbinary
- Nonbinary people might have lower hormone level goals which could influence bone health considerations

"*There is something twisted about the way society has historically viewed transgender people, people who are gender incongruent, gender diverse, gender queer. We're seen through prisms of ingrained beliefs about the human condition, most of which are already distortions of facts. Each of us must learn to find ourselves, then to accept ourselves, and then to find our place in the world.*"

- Jamison Green, Ph.D. Author, educator, activist, past president of the World Professional Association for Transgender Health (WPATH), current co-chair of WPATH Ethics Committee

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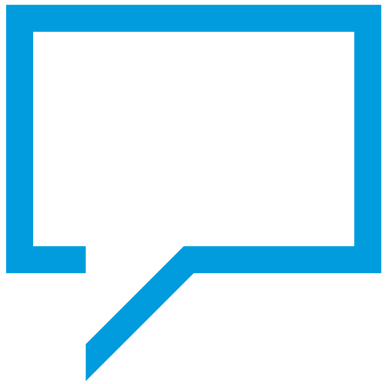
QUESTIONS & DISCUSSION



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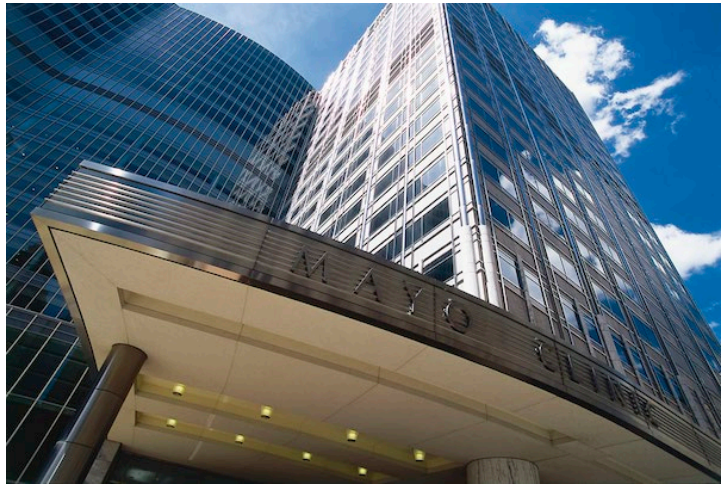
THANK YOU FOR JOINING US IN THIS COURSE



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