

Prospective Cohort Study to Assess Long-Term Effect of Puberty-Suppressing Medication on Bone Health

It is becoming more and more common for transgender youth to be treated with puberty-suppressing medications in order to stall the development of unwanted secondary sex characteristics until the age of 16, when they can formally consent to cross-sex hormone replacement therapy [2]. Previous medical research shows that commonly used hormone-blocking medications such as gonadotropin releasing hormone (GnRH) may cause a temporary reduction in bone mineral density [1,4,7,8]. Short-term studies have shown that this effect is reversible [5,6], but it is not known whether these medications have any long-term effect on bone health. We propose a prospective cohort study that will assess the long-term effect that puberty-suppressing medications have on bone health.

Sex hormones play a pivotal role in healthy skeletal development during early adolescence and an equally important role in the maintenance of bone health and metabolism later in life [17]. During puberty, adolescents will experience a 40-50% increase in bone mass and will typically achieve 85-90% peak bone mass by the age of 17 [15]. Moreover, peak bone mass is considered to be a major determinant of negative health outcomes such as bone fractures and osteoporosis [7,14]. With this in mind, some clinicians are justifiably concerned that the medicinal suppression of puberty in adolescents may contribute to an increased likelihood of adverse health effects in the long-term [12,18].

Several long-term follow-up studies have been conducted on adult transsexuals to assess the effect of GnRH analogues on body composition and bone mineral density, however, in these studies GnRH was routinely administered in conjunction with a cross-sex hormone regimen, making it difficult to tease out the effect of GnRH alone [9,10,13,14,16,19]. In addition, since these studies focused only on subjects who had been treated in adulthood, they make no claim regarding the effect of GnRH analogues on critical bone development. A small number of follow-up studies have been conducted on puberty suppression in adolescents, but so far they have all concentrated on emotional and psychological outcomes [4,8]. There is one exception to this trend in the literature in which researchers conducted a 22-year follow-up study on a single female-to-male transsexual who had been treated with GnRH analogs at 13 years of age [3]. The researchers reported that the subject's bone mineral density and height were both within the 50th percentile for biological males and for biological females, suggesting that puberty suppression did not have a negative effect on skeletal development [3]. In this critical area of modern pediatric medicine, there is clear need for a larger and more generalizable investigation.

The specific goal of our study will be to test the hypothesis that continuous exposure to GnRH in adolescence leads to a significant reduction in peak bone mass (PBM). Participants in our study will be selected from adolescents aged 8 to 18 who are receiving gender counseling at one of three youth clinics: the Gender Management Services Center (GEMS) at Boston Children's Hospital, the Child and Adolescent Gender Center Clinic (CAGC) at Benioff Children's Hospital, and the Center for Transyouth Health and Development (CTHD) at the

Children's Hospital Los Angeles. Parents will have the option to enroll their adolescent in the study over a period of five years, after which the group of participants in our study will be finalized. The exposure group will contain those individuals who have been treated with GnRH before the age of 18 for a period lasting longer than six months. The comparison or control group will be comprised of individuals who have not received any treatment with GnRH. With this division, the exposure status of each participant is free to change until they reach 18 years of age, at which point they are permanently settled into a cohort. Participants who are treated with GnRH for a period of time lasting less than six months prior to age 18 will be removed from the study due to their ambiguous exposure status.

When each member of the exposure group reaches 18 years of age, we will collect from them the following information: age at initial administration of GnRH, peak dosage level, total length of time on GnRH, race, and assigned sex at birth. All information regarding puberty-suppressing medication will be verified from medical records. Each member of the control group will have their race and assigned sex at birth recorded. Participants in both groups will be brought in for medical examinations a total of four times over a period of twelve years. Starting at age 18, each participant will be examined once every four years by an approved orthopedist who will conduct a dual-energy x-ray absorptiometry (DXA) test to measure their bone mineral density (BMD). In addition, at the time of medical testing, each participant will be interviewed to determine whether or not they had initiated cross-sex hormone replacement therapy (HRT) in the interim. This information will be verified via medical records and each cohort will be subdivided based on the participant's answer to this question. Furthermore, the participants will be asked a series of questions regarding their current lifestyle, such as their overall nutritional habits, regularity of physical activity, and their status as a smoker. As an incentive, each participant will receive a \$50 Amazon gift card at the end of the interview and the medical examinations will be conducted free of charge.

The outcome of the study will be an adjusted relative risk of reduced PBM that will be computed from the the fourth and final measurements of BMD. These measurements will be conducted on each participant at age 30, which is believed to be roughly the age at which PBM is achieved [17]. The PBM of members in each exposure subgroup will be compared with their corresponding control subgroup: (GnRH + HRT) compared with (No GnRH + HRT) and (GnRH + No HRT) compared with (No GnRH + No HRT). Furthermore, participants will be matched according to five criteria: assigned sex at birth (male / female), race (African American / Not African American), overall nutritional habits (rated good / poor), overall level of physical activity (rated high / low), and lifetime status as a smoker (rated yes / no). The subjective ratings are to be assigned by the researcher based on the four responses to these questions received from the participant over the twelve year period. Each criterion is known to have an effect on PBM [11], so we match participants accordingly to avoid potential confounding.

The main strengths of our study are that we have a high level of control over the quality and quantity of our data and that we have the ability to definitively establish a temporal relationship between the exposure to GnRH in adolescence and the outcome of reduced PBM. In

addition, we uniquely have the ability to disentangle the effects of GnRH from the effects of cross-sex hormone replacement therapy. Our results are intended to be generalizable to the vast majority of adolescents that are suffering from gender dysphoria. The conclusions that will be drawn from our investigation will fill in an unacceptably large gap in our knowledge regarding the long-term health outcomes of an increasingly common adolescent treatment plan. Ultimately, this study will assist healthcare providers in making the best possible treatment decisions for transgender youths.

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