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

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ABSTRACT

Puberty is highly important for the accumulation of bone mass. Bone turnover and bone mineral density (BMD) can be affected in transgender adolescents when puberty is suppressed by gonadotropin-releasing hormone analogues (GnRHa), followed by treatment with cross-sex hormone therapy (CSHT). We aimed to investigate the effect of GnRHa and CSHT on bone turnover markers (BTMs) and bone mineral apparent density (BMAD) in transgender adolescents. Gender dysphoria was diagnosed based on diagnostic criteria according to the DSM-IV (TR). Thirty four female-to-male persons (transmen) and 22 male-to-female persons (transwomen)were included. Patients were allocated to a young (bone age of <15 years in transwomen or <14 in transmen) or old group (bone age of ≥15 years in transwomen or ≥14 years in transmen). All were treated with GnRHa triptorelin and CSHT was added in incremental doses from the age of 16 years. Transmen received testosterone esters (Sustanon, MSD) and transwomen received 17-β estradiol. P1NP, osteocalcin, ICTP and BMD of lumbar spine (LS) and femoral neck (FN) were measured at three time points. In addition, BMAD and Z-scores were calculated. We found a decrease of P1NP and 1CTP during GnRHa treatment, indicating decreased bone turnover (young transmen 95% CI −74 to −50%, $p = 0.02$, young transwomen 95% CI −73 to −43, $p = 0.008$). The decrease in bone turnover upon GnRHa treatment was accompanied by an unchanged BMAD of FN and LS, whereas BMAD Z-scores of predominantly the LS decreased especially in the young transwomen. Twenty-four months after CSHT the BTMs P1NP and ICTP were even more decreased in all groups except for the old transmen. During CSHT BMAD increased and Z-scores returned towards normal, especially of the LS (young transwomen CI 95% 0.1 to 0.6, $p = 0.01$, old transwomen 95% CI 0.3 to 0.8, $p = 0.04$). To conclude, suppressing puberty by GnRHa leads to a decrease of BTMs in both transwomen and transmen transgender adolescents. The increase of BMAD and BMAD Z-scores predominantly in the LS as a result of treatment with CSHT is accompanied by decreasing BTM concentrations after 24 months of CSHT. Therefore, the added value of evaluating BTMs seems to be limited and DXA-scans remain important in follow-up of bone health of transgender adolescents.

1. Introduction

Puberty is the most important period in life regarding the accumulation of bone mass. In general, about 85%–90% of the total bone mass will have been acquired at the end of puberty [1]. Sex steroids reach high concentrations as puberty progresses and play a key role in the augmented bone growth and bone mass accumulation in adolescents. Consequently, the process of bone turnover, bone remodelling and bone mineral apposition increase during puberty as well [2]. In adolescents with gender dysphoria the pubertal development of secondary sex characteristics during puberty can cause psychological distress because

Abbreviations: BMD, bone mineral density; BMAD, bone mineral apparent density; BTM, bone turnover marker; GnRHa, gonadotropin-releasing hormone analogue; CSHT, cross-sex hormone therapy; Female-to-male persons, transmenMale-to-female persons = transwomen; GA therapy, gender affirming therapy; FN, femoral neck; LS, lumbar spine.

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this physical maturation belongs to their unwanted sex assigned at birth. When transgender adolescents are treated, the first step of the so-called gender affirming (GA) therapy is the administration of gonadotropin-releasing hormone analogues (GnRHa) to suppress puberty. The GnRHa treatment induces a hypogonadal state, resulting in a developmental arrest of the undesired secondary sex characteristics of the sex assigned at birth [3–5]. Bone metabolism is affected by the GnRHa treatment as well and as a result the BMD as measured by DXA-scan can decrease [6–7]. The second step of the GA therapy of transgender adolescents consists of gender affirming hormones also known as cross-sex hormone therapy (CSHT) from the age of 16 years. The purpose of CSHT is to induce the development of secondary sex characteristics of the desired sex. Until now the effects of CSHT on both BMD and bone turnover in transgender adolescents are not known [6,8,9].

Bone turnover markers (BTMs) can be used to display the actual bone metabolism in transgender adolescents. Several studies show that BTMs reach high concentrations during biological puberty [10–12]. To date, there is little data on the course of BTMs in relation to BMD during pubertal suppression and treatment with CSHT in transgender adolescents. When GA therapy affects the bone quality during puberty this might have an impact on the bone quality in later adult life, especially with regard to a possible lower BMD and the risk of osteoporosis and fractures. Hence, studies are needed to assess both the immediate and the long-term effects of the GA therapy on bone metabolism in transgender adolescents.

The objective of this study is to investigate the course of three bone turnover markers in relation to bone mineral density, in transgender adolescents during gonadal suppression and during CSHT.

2. Methods

2.1. Subjects and treatment protocol

Adolescents diagnosed with gender dysphoria who were treated with GnRHa and CSHT were recruited at our clinic the Centre of Expertise on Gender dysphoria at the VU University Medical Centre, Amsterdam, the Netherlands. Gender dysphoria was diagnosed based on diagnostic criteria according to the DSM-IV (TR) [13]. This retrospective study was approved by the Ethical Committee of the VU University Medical Centre and data collection started only after the subjects and their parents or legal representatives provided written consent. Data for this study was collected at three moments in time: (1) D0: at start of GnRHa treatment to suppress puberty, (2) C0: at start of CSHT and (3) C24: at 24 months after C0.

Inclusion criteria of this study were: adolescents with diagnosed gender dysphoria, a serum BTM measurement of P1NP, osteocalcin or carboxy terminal cross linked telopeptide of type I collagen (ICTP) within 90 days before or after time point D0, C0 and C24, and/or a DXA-scan of the lumbar spine (LS) and/or femoral neck (FN) performed within 90 days before or after time point D0, C0 and C24. After applying these criteria to an eligible patient group of 85 transwomen (male-to-female persons) and 130 transmen (female-to-male persons) a cohort of 28 transwomen and 42 transmen were included in the study. The full treatment protocol and all clinical assessments were extensively described previously [6]. Briefly, the GA therapy of transgender adolescents starts with administration of GnRHa triptorelin (Decapeptyl – CR ®, Ferring) 3.75 mg subcutaneously every 4 weeks in order to suppress puberty of the sex assigned at birth (D0). In transmen triptorelin starts from Tanner B stage 2 or more and in transwomen when the testicle volume is at least 6–8 mL or when Tanner G is staged at 2 or 3. CSHT, the second phase of GA therapy, starts from the age of 16 year (C0) transmen receive testosterone esters (Sustanon ®, MSD), with an initial dose of 25 mg/m^2 body surface area IM every two weeks and doses are increased every 6 months until an adult maintenance dosage of 250 mg every 4 weeks is reached. The transwomen are treated with 17-β-estradiol orally, with an initial dose of 5 μg/kg daily with 6-monthly increments until an adult maintenance dosage of 2 mg daily.

All 28 transwomen and 42 transmen which were included in this study started the GA therapy between 2001 and 2011. The patients were categorised into a young and old pubertal group, based on their bone age. The young transmen had a bone age of <14 year and the old transmen had a bone age of ≥14 years. The young transwomen group had a bone age of <15 year and the old transwomen group ≥15 years. These groups were created to account for the difference between biological age and pubertal stages of the adolescents as the older patients already partially completed their puberty, resulting in higher bone mass accrual compared to younger patients. Groups were based on the median bone age of the groups and also because the peak height velocity ages were reached earlier and as a result the near-final height was reached at these respective bone ages. The bone age was measured by a X-ray of the left hand and was assessed using the method of Greulich and Pyle [14].

2.2. Measurements

2.2.1. General

Body weight and height were measured each visit (D0, C0 and C24). A wall-mounted Harpenden Stadiometer was used to measure the standing height and weight without shoes on. The stages of pubertal development were assessed according to Tanner by a paediatrician-endocrinologist each visit.

2.2.2. Bone turnover markers

The formation markers P1NP and osteocalcin and the resorption marker ICTP were measured in non-fasting state. P1NP was measured using a RIA (Orion Diagnostica, Espoo, Finland) with an intra-assay coefficient of variation (CV) of 4–8% and inter-assay CV of 8%. The lower limit of quantitation (LOQ) was 5 μg/L. Osteocalcin was measured using an immunometric-assay (Biosource, Nivelles, Belgium) with an intra-assay CV of <5%, inter-assay CV of 8–15% and LOQ of 0.4 nmol/L. ICTP was measured using a RIA (Orion Diagnostica, Espoo, Finland) with an intra-assay CV of 4–6%, inter-assay CV of 7% and LOQ of 1 μg/L.

2.2.3. Bone densitometry (DXA-scan)

A DXA-scan (Hologic QDR 4500, Hologic Inc., Bedford, MA, USA) with a precision of <1% was used to measure BMD in g/cm^2 of the LS and FN of the non-dominant hip. The LS and FN were the anatomical sites of choice as reference values for BMD and BMAD of these regions in adolescents were studied before [15]. To correct for height and height gain the volumetric bone mineral apparent density (BMAD) in g/cm^3 for both LS and FN was calculated. BMAD Z-scores were calculated for sex assigned at birth using an UK reference population, due to the lack of consensus with regard to the use of either sex assigned at birth or desired sex reference values in transgender adolescents [15]. The lack of validated reference values of bone age needed to calculate the BMAD and Z-scores limits the use of bone age and therefore the chronological calendar age of the transgender adolescents was used. Furthermore, the reference values of L- M- and S-values of 17 year old biological males and females were used to calculate the BMAD for patients older than 17 year, due to the lack of reference values of adolescents exceeding the age of 17 years [15,16].

2.3. Statistics

Stata/SE 13.0 software (StataCorp, LP) was used for calculations and statistical analysis. Normality was tested by normality plots and by Shapiro-Wilk tests. As described previously patients were categorised in different groups based on sex and bone age resulting in four groups: young transmen, old transmen, young transwomen and old transwomen. Further sub analyses were not possible due to the limited sample size. Wilcoxon signed rank tests were used to analyse the non-