Bone and Mineral Metabolism

CLINICAL ASPECTS OF OSTEOPOROSIS AND VITAMIN D ACTION

Evaluation of Bone Mass in Transgender Women After Gender Affirming Surgery - a Pilot Study

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MON-393

Estrogen deficiency is classically associated with bone loss in both men and women. In transgender women, after being submitted to gender-affirming surgery (GAS), the main goal of hormone therapy (HT) is to maintain the female phenotype and prevent the consequences of the orchietomy-related hypogonadal state. The aim of this study was to evaluate the impact of GAS on bone mass in transgender women. A total of 142 trans women attending the outpatient Gender Identity Program were sequentially enrolled. Patients aged < 20 and > 60 years (n=15), with gluteal silicone prosthesis (n=26) and without FSH dosage after surgery (n=9) were excluded. Anthropometric evaluation, laboratory tests and dual-energy X-ray absorptiometry (DXA) were performed in all patients during the follow-up. In women undergoing CAS (CAS-Y), DXA was performed at least 12 months after surgery and with estrogen therapy. In the other women (CAS-N), tests were performed after at least 3 months of standardization treatment (estradiol plus spironolactone or cyproterone acetate). Patients with testosterone values still above the reference for women were not excluded as long as they were on regular HT. Ninety two trans women were included. Among them, 30 had performed CAS, and had DXA assessment performed 37 months (21-78) after surgery. The mean age and BMI were 37 years (33 - 46) and 24.9 kg/m² (23.1 - 27.5) in patients CAS - Y and 30 years (24 - 36) and 24.3 kg/m² (21.5 - 28.5) in patients CAS - N. Trans women CAS-Y were significantly older (p=0.000). There was no difference observed regarding estradiol levels between the groups [105.7pmol/L (48.4-207.8) and 147.5 pmol/L (71.9-284.5), p=0.622]. Free androgen index (FAI) was significantly higher [0.45 (0.17 - 1.63) and 4.47 (0.70 - 36.4), p=0.002] and FSH significantly lower [60.4mIU/ml (37.9 - 75.6) and 2.6mIU/ml (0.6 - 4.4), p=0.000] in trans women CAS - N. BMD (g/cm²) and Z-score of lumbar spine, femoral neck and total femur did not differ significantly between the groups. Considering all participants, the lumbar spine BMD was negatively correlated with FSH levels (r=-0.343, p=0.005), which remained significant even after adjustments for FAI. When only CAS - Y trans women were considered, a negative correlation was found between FSH levels and lumbar spine (r=-0.598, p=0.001) and hip (r=-0.404, p=0.033) BMD. In a multiple regression model adjusted for age and surgery, women with FSH > 35 mIU/ml presented a prevalence rate ratio of 11.79 for low bone mass (p=0.040, IC 95% 1.19 - 124.39). The results of this pilot study in trans women show no difference in bone mass according to GAS status. However, long-term elevated FSH levels observed in some post GAS - trans women, even on HT, presented a negative association with bone mass. Further studies with greater sample sizes are needed to confirm the impact of GAS on bone mass and fracture risk.

Bone and Mineral Metabolism

BONE AND MINERAL CASE REPORTS II

Low Bone Mineral Density Does Not Equal Osteoporosis: The Finding of XLHR with a Novel Phex Mutation.

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MON-373

Introduction: X-linked Hypophosphatemic rickets (XLHR) is a rare form of rickets that mainly affects children but, in some cases, it can be missed and not diagnosed until later in life. We present a post-menopausal female that was misdiagnosed with osteoporosis for many years until complete work up was done, and she was found to have osteomalacia due to hypophosphatemia. Clinical case: A 59-year-old female was evaluated following admission to the hospital for a worsening femur fracture on imaging and had received ORIF. She was diagnosed with osteoporosis at the age of 45 and endorses a history of multiple femur fractures from low impact trauma. Despite previous bisphosphonate therapy, she continued to have recurrent fractures.[RC1] She reported no family history of early osteoporosis, but her mother was diagnosed with rickets as a child. Secondary workup for osteoporosis revealed normal 25OH vitamin D, SREP, TSH, PTH and serum calcium, endomysial antibodies, and 24-hour urine calcium levels. However, the patient had persistently elevated alkaline phosphatase levels (150-200) and low phosphate levels (1.8-2.4). This raised the possibility of Paget’s disease, so a bone scan and lumbar X-ray were obtained which were normal. Given low phosphate levels, fibroblast growth factor (FGF)-23 was obtained and was elevated. This left the differential between tumor-induced osteomalacia (TIO) significantly lower [60.4mIU/ml (37.9 - 75.6) and 2.6mIU/ml (0.6 - 4.4), p=0.000] in trans women CAS - N. BMD (g/cm²) and Z-score of lumbar spine, femoral neck and total femur did not differ significantly between the groups. Considering all participants, the lumbar spine BMD was negatively correlated with FSH levels (r=-0.343, p=0.005), which remained significant even after adjustments for FAI. When only CAS - Y trans women were considered, a negative correlation was found between FSH levels and lumbar spine (r=-0.598, p=0.001) and hip (r=-0.404, p=0.033) BMD. In a multiple regression model adjusted for age and surgery, women with FSH > 35 mIU/ml presented a prevalence rate ratio of 11.79 for low bone mass (p=0.040, IC 95% 1.19 - 124.39). The results of this pilot study in trans women show no difference in bone mass according to GAS status. However, long-term elevated FSH levels observed in some post GAS - trans women, even on HT, presented a negative association with bone mass. Further studies with greater sample sizes are needed to confirm the impact of GAS on bone mass and fracture risk.
vs hypophosphatemic rickets. Ga-DOTATE scan and PET scan were negative, so the patient subsequently underwent genetic testing. She was found to have a mutation in the enzyme regulating endopeptidase homologue (PHEX) gene mutation and was finally diagnosed with XLHR. Her PHEX mutation was caused by a novel variant, c.1366 T>C or W456R, which has only been documented once in the literature. The patient was treated with 2 gm per day of phosphate supplementation in divided doses and calcitriol 0.25 mcg once daily which normalized her phosphate and 1.25 vitamin D levels. 1 month later after treatment, she reported significant improvements in bone pain, and her DEXA scans were stable for the following 4 years. Discussion: XLHR is a heterogeneous group of inherited disorders characterized by hypophosphatemia and impaired bone mineralization leading to rickets. It results from mutations affecting the PHEx gene of which more than 300 pathogenic variants have been described. The mutation causes excess FGF-23 which leads to osteomalacia and chronic hypophosphatemia. This condition can be difficult to distinguish from TIO as both present with low phosphate and elevated FGF-23 but can be differentiated with genetic testing. Recognition of the correct diagnosis is prudent to providing correct treatment. The current treatment for XLH is calcitriol and phosphorus replacement. Recently, burosumab was FDA approved in 2018 for treatment in adults.

Genetics and Development (including Gene Regulation)

GENETICS AND DEVELOPMENT AND NON-STEROID HORMONE SIGNALING II

Restoration of Growth and Fertility in Zebrafish (Danio Rerio) Model with PROP1 Knockout Generated by CRISPR/Cas9 Genomic Editing.

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MON-712

Introduction: Hypopituitarism is defined as the deficiency of one or more pituitary hormones and can occur due to pathogenic allelic variants in transcription factors involved in pituitary development. PROP1 gene is responsible for progenitor cell migration from the marginal zone to the anterior lobe, and its terminal differentiation into corticotropes and gonadotropes cell lines besides somatotropes, lactotropes and thyrotropes due to POU1F1 (also known as PIT1) activation. In humans, mutations in the PROP1 gene are the most common cause of congenital hypopituitarism with GH, TSH, LH/FSH, and progressive ACTH deficiencies. A dwarf phenotype with short stature, pituitary hormone deficiency, and infertility has been described in humans and Ames mice lineage harboring mutations in the PROP1/Prop1 gene. Another valuable animal model used in basic research is the zebrafish (Danio rerio) due to a high homology in neuroendocrine functioning. To test the potential of this model, in our previous study, a 32bp insertion carrying a stop codon was directed into the second exon of prop1 with CRISPR/Cas9, establishing a homozygous mutant strain (prop1mut). Objective: To characterize the phenotype and expression patterns of transcription factors and hormones in the zebrafish prop1mut lineage. Methods: prop1, pit1, and gh1 mRNA levels were analyzed during embryonic development at 24 and 72 hours post-fertilization (hpf). RNA from 30 pooled embryos was extracted using DirectZol RNA Miniprep. cDNA was synthesized from 1ug of total RNA using High-Capacity cDNA Reverse Transcription Kit and qPCR was performed using SYBR Green PCR Master Mix. Gene expression was normalized to ef1a and the prop1mut group was compared with the control wild type group (WT). Animals were kept in the tanks at a density of 15 animals/liter and were acquired at 13 and 20 days post fertilization (dpf) after brief anesthetization using a stereomicroscope and measured in ImageJ software to determine the larval standard length from nose to the end of the spinal cord. Results: At 24 and 72hpf, prop1mut embryos expressed the altered prop1 mRNA at similar levels to the prop1 expression observed in WT. Lower pit1 expression in prop1mut embryos was observed at both periods (p<0.01). Albeit in lower levels, similar gh1 expression was observed in both lineages at 24hpf, and prop1mut embryos presented lower gh1 expression at 72hpf (p<0.001). prop1mut larvae presented a significant decrease in size at 13dpf (p<0.001) but not at 20dpf. Conclusion: In this study, the prop1mut zebrafish model exhibited a dwarf phenotype during larval development associated with diminished pit1 and gh1 expression during the embryonic stage. Additionally, in the juvenile stage, the development rate in prop1mut animals was restored, presenting similar standard lengths observed in WT animals.

Adipose Tissue, Appetite, and Obesity MECHANISMS AND TREATMENT OF OBESITY IN HUMANS

ARNT2: A Potential Novel Candidate Gene for Monogenic Obesity in Humans

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OR33-07

Introduction: Aryl hydrocarbon nuclear translocator 2 (ARNT2) is a basic helix-loop-helix (bHLH)-PAS (Per/Arnt/Sim) transcription factor shown to be critical to the development of paraventricular nucleus of the hypothalamus (PVN), key region for energy homeostasis and feeding response. In vivo and in vitro studies have shown that ARNT2 is an obligate heterodimer for SIM1, known cause of monogenic obesity. Null mutations in Arnt2 in animals are not viable, but hypomorphic mutation results in hyperphagic