MON-382

Background: Obesity and type 2 diabetes mellitus (T2DM) are both associated with normal to above average bone mineral density (BMD) but increased risk of fragility fractures. The impact of T2DM on bone mechanical and microarchitectural features in the obese population is unknown. We hypothesize that obese diabetics have lower bone quality compared to obese nondiabetic individuals. In this study, we investigated the microarchitectural features and mechanical properties of bone of obese men with and without T2DM along with the independent predictors of bone strength. **Methods**: Ninety-seven obese men (BMI >30) aged 35-65 years-old of which 38 had T2DM were included in the analysis. BMD and body composition were evaluated by DXA and bone microarchitecture of the tibia by high-resolution peripheral quantitative computed tomography. Bone strength was assessed by micro finite element analysis-derived parameters as failure load (f. load) and stiffness. Serum testosterone and estradiol were measured by LC-MS. Serum SHBG, osteocalcin (OCN), C-telopeptide (CTx) and sclerostin (SCL) were measured by ELISA. **Results:** OCN is lower in obese men with T2DM compared to those without T2DM (4.8 ± 2.8 vs 6.2 ± 2.6 ng/mL p=0.03, respectively), with also a trend for reduced CTx and SCL in the former. BMD at all sites was reduced in obese men with T2DM, but there were no differences in body composition. Obese diabetics also had lower tibial total volumetric BMD (vBMD) (p=0.04) and trabecular vBMD (p=0.01) with greater trabecular spacing (p=0.005). F. load (13.3 ± 2.1 vs 14.5 ± 2.3 kN, p= 0.02) and stiffness (24.7± 4.2 vs 27 ± 4.6 kN/mm, p=0.02) were reduced in men with T2DM relative to men without T2DM, respectively. F. load and stiffness were positively correlated with BMD at all sites, fat free mass (FFM), lean mass, free testosterone, free estradiol and SCL, but negatively correlated with % total body fat and visceral adipose tissue (VAT). FFM, BMD of the total hip, femoral neck and lumbar spine and free testosterone were significant independent predictors of bone strength in the entire group (model: R^2: 65.01 p< 0.0001 for f. load and model: R^2:63.21 p < 0.0001 for stiffness), whereas age and lumbar spine BMD were found to be independent predictors of bone strength in the non-diabetic group (model R^2: 54.6 p< 0.0001 for both f. load and stiffness). Analysis limited to the diabetic subgroup showed that BMD at the femoral neck and total hip, % total body fat, VAT volume, SCL and free estradiol were independent predictors of bone strength (model: R^2: 88.4 and p< 0.0001 for f. load and model: R^2: 85.3 and p<0.0001 for stiffness). Interleukin-6 was comparable between groups. **Conclusions**: Obese men with T2DM have lower bone formation and impaired bone quality and strength compared to those without T2DM. In addition to BMD and gonadal hormones, adiposity is an important predictor of bone strength in obese men with T2DM.

Reproductive Endocrinology

CLINICAL STUDIES IN FEMALE REPRODUCTION I

Adrenal Androgen Production Is Maintained While Ovarian Estrogens Fall Following the Final Menstrual Period in the Study of Women's Health Across the Nation (SWAN)

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SAT-022

The aim of this study was to clarify changes in sex steroids at the final menstrual period (FMP). We have shown previously that estradiol (E2) declines substantially in the 4-year period around the FMP, but hypothesize that testosterone (T) declines modestly and adrenal Δ5 androgens dehydroepiandrosterone (DHEA) and androstenediol (Adiol) remain unchanged. **Methods:** Liquid chromatography tandem mass spectrometry (LC-MS/MS) and immunoassay was used in approximately annual samples collected before and following FMP in 1490 women. We estimated time-related changes in each log-transformed androgen using piecewise linear mixed modeling, with knots (slope changes) at FMP-2 yrs and FMP+2 yrs as seen for E2. These models then were re-estimated for subgroups with different time courses identified using group-based trajectory modeling. **Results:** In the full sample, T was generally stable, although time course varied by subgroup, with a significant decrease of 5%/year in T in [FMP-2yrs, FMP+2yrs] only in the lowest T women. For DHEA and Adiol, declines were similar across all 3 time segments and across subgroups. Mean circulating androgen concentration declined modestly (P> 0.05) from five years before to five years following FMP. However, when stratified only the lowest 7% of circulating T declined significantly (p< 0.05) in the four years surrounding FMP when mean circulating E2 declined. This trajectory divergence of the lower circulating T suggests a different, non-adrenal source that is decreased at FMP which may be useful in clarifying ovarian versus adrenal testosterone production during the post-menopause. Paired results from samples collected before and following FMP in the same subjects indicate mean circulating E2 is less than 5% of mean circulating T suggesting that a relatively large portion of circulating E2 may be largely a result of peripheral conversion of adrenal androgens. Longitudinal LC-MS/MS analyses of circulating E2 and T indicate that the principal change in sex steroid influence at menopause is largely a decrease and dampening of ovarian and not adrenal steroid production.

Genetics and Development (including Gene Regulation)

GENETICS AND DEVELOPMENT AND NON-STEROID HORMONE SIGNALING I

Clinical and Genetic Features of Families with Maternally Inherited Central Precocious Puberty

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SUN-725

Context: The clinical recognition of familial central precocious puberty (CPP) has significantly increased in the last years. This fact can be related to the recent descriptions of genetic causes associated with this pediatric condition, such as loss-of-function mutations of two imprinted genes (*MKRN3* and *DLK1*). Inherited defects in both genes cause paternally inherited CPP. However, no genetic abnormality has been described in families with maternally inherited CPP so far.
Objectives: To characterize the clinical and genetic features of several families with maternally inherited CPP.
Setting and Participants: We analyzed clinical and genetic features of children with familial CPP. No brain MRI alterations were detected in the selected patients with CPP. *MKRN3* and *DLK1* pathogenic mutations were excluded. Whole-exome sequencing was performed in selected cases.
Results: We studied 177 children from 141 families with familial CPP. Paternal inheritance was evidenced in 44 families (31%), whereas 58 (41%) had maternally inheritance. Indeterminate inheritance was detected in the remaining families. Maternally inherited CPP affected mainly female patients (69 girls and two boys). Thelarche occurred at mean age of 6.1 ± 1.9 years in this female group. Most of girls had Tanner 3 (41%) and Tanner 4 (35%) breast development at first evaluation. One boy had additional syndromic features (macrosomia, autism, bilateral eyelid ptosis, high arcade palate, irregular teeth and abnormal gait). The pedigree analysis of patients with maternally inherited CPP revealed the following affected family members: 42 mothers, 10 grandmothers, 11 sisters, 12 aunts, and 11 female cousins. Most of the families (41) had two affected consecutive generations, while eight families had three affected generations. No consanguinity was referred. Ongoing molecular analysis revealed two rare heterozygous variants in the boy with syndromic CPP and three affected family members with precocious menarche (mother, maternally half-sister, and maternally aunt): a frameshift deletion (p.F144fs) in *MKKS*; and a missense variant (p.P267L) in *UGT2B4*, which encodes a protein involved in estrogen hydroxylation and it was related to menarche timing in genome-wide association studies.
Conclusions: Maternally inherited CPP was diagnosed mainly in girls, who had thelarche at mean age of 6 years old. Dominant pattern of inheritance was more prevalent, with direct maternal transmission in 72% of the studied families. New candidate genes might be implicated with maternally inherited CPP.

Thyroid

THYROID DISORDERS CASE REPORTS II

Response to Tocilizumab Retreatment in Refractory Thyroid Eye Disease

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SAT-500

Background: The current standard of care for moderate to severe thyroid eye disease (TED) is intravenous methylprednisolone (IVMP), though alternative immunosuppressive options are emerging. In a recent randomized trial, Tocilizumab (TCZ), an anti-IL-6 receptor antibody, demonstrated improved efficacy for corticosteroid-resistant TED compared to placebo. Clinical response to TCZ retreatment, however, has not been previously reported.
Clinical case: A 64-year old man presented with progressive diplopia, eyelid retraction and edema and retrobulbar pain. Initial labs revealed TSH 0.221 uIU/mL, free thyroxine (FT4) 1.11 ng/dL, total T3 172 ng/dL and a thyroid stimulating immunoglobulin (TSI) index of 329 (normal < 140). The patient was a former cigarette smoker who had recently transitioned to e-cigarettes. He was treated with 12 weeks of IVMP with improvement in ocular redness and swelling. Three months following completion of treatment, he presented with worsening left sided proptosis, restrictive strabismus, and compressive optic neuropathy (CON) evidenced by deteriorating central acuity and color vision. He underwent urgent surgical decompression for CON with full restoration of visual acuity. He then received a second 12-week course of IVMP with concomitant orbital radiation. Of note, his hyperthyroidism was well controlled with methimazole. Two months after his second IVMP course, he had a third flare of ophthalmic symptoms. He was then treated with TCZ 8 mg/kg (800mg) IV monthly for six months. The patient's Clinical Activity Score (CAS) improved from 4 to 2 and TSI index decreased from 610 to 92 (normal). He had significant improvement in periorbital edema, caruncle/plica swelling, and conjunctival injection. However, ten months following completion of the TCZ course he again complained of worsening diplopia and left proptosis. Of note, relapse of his TED symptoms was preceded by an increase in TSI from 92 to 300 two months prior. Orbital CT demonstrated progression of left orbitopathy and increased orbital apex crowding. Following these CT findings he was restarted on TCZ, of which he has now completed 5 additional infusions. His CAS has improved from 3 to 2 and TSI index has decreased from 284 to 100.
Conclusion: This is the first reported case of response to successive courses of TCZ in relapsing, severe, corticosteroid-resistant TED. TCZ can be an effective option for refractory TED though retreatment may be necessary for recurrent inflammation. Further study of TCZ is required to determine its role in relapsing TED and the optimal duration of therapy needed.
References:
Perez-Moreiras et al., 2018. Efficacy of Tocilizumab in patients with moderate to severe corticosteroid resistant Graves' orbitopathy: a randomized controlled trial. Am J Ophthalmol 195:181

Reproductive Endocrinology

REPRODUCTIVE ENDOCRINOLOGY: REPRODUCTIVE FUNCTION AND DYSFUNCTION ON DEVELOPMENT

Prenatal Anti-Mullerian Hormone (pAMH) Exposure in Mice Induces Changes in Pubertal Onset, Fertility, and Stress Response in Both Male and Female Offspring

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