models accurately address the cascade of effects that follow ovarian hyperandrogenism. **Aim:** Here, we aim to study the specific effects of hyperandrogenemia on ovarian morphology, follicle function and fertility with a new transgenic (TG) mouse model expressing elevated Cyp17 levels exclusively in TCs. **Methods:** We generated a breeding line of triple TG mice using a combination of the Tet-dependent expression system and the Cre/LoxP gene control system. Specifically, we used Cyp17 promoter-iCre mice crossed with trans-activator mice (R26-STOP-rtTA-IRES-EGFP transgene, Jackson Lab) and with a responder mouse carrying the TRE-Cyp17 transgene. Cyp17 promoter-iCre mice were used to ensure rtTA/EGFP is expressed specifically in TCs of secondary follicles. After the DNA segment between the two LoxP sites is excised by Cyp17iCre specifically in TCs, the R26-STOP-rtTA gene remains activated in all daughter TCs. Only upon treatment with Doxycycline (DOX) can suppression be relieved and active transcription of TRE-Cyp17 be induced in a dose-dependent manner. **Results:** Cyp17 mRNA expression levels in TCs of TG mice treated with 20, 100 or 200 mg/Kg DOX compared with corresponding untreated control mice showed a modulation in a dose-dependent manner (P=0.01 ANOVA). Confocal and RNAscope analysis validated (i) the effective combination of the Cyp17iCre/rtTA expression system visualizing the rtTA/EGFP specifically expressed in ovarian TCs and (ii) the DOX-induced increase of Cyp17 expression compared with the WT mice. DOX treated TG females were acyclic, being mostly arrested in diestrus. Analysis of estrous cycle stages revealed that treated TG females spent significantly more time in diestrus than control females (P=0.007, ANOVA). **Conclusions:** Our new *in vivo* model is the first that analyzes androgen impact independent of any extraovarian source of androgen, complementing current clinical efforts to study the occurrences of TCs elevated androgen levels in normal and PCOS women. 1 Rosenfield, R. L. *et al. Endocr Rev* (2016)2 Azziz, R. *et al. Nat Rev Dis Primers* (2016)3 Comim, F. V., *et al. Hum Reprod* (2013)4 Stener-Victorin, E. *et al. Endocr Rev* (2020)

Reproductive Endocrinology

OVARY, TESTES, AND IMPACT OF HORMONES ON METABOLIC FUNCTION

Abnormalities in Microarchitecture and Reduced Mechanical Bone Strength in a Rat Model of Polycystic Ovary Syndrome

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Evidence from the literature is contentious about the impact of polycystic ovary syndrome (PCOS) on the skeleton, suggesting a possible negative role of this condition on non-obese women. We investigated this hypothesis employing a well-characterized testosterone propionate (TP) rodent model of PCOS to address the consequences of androgenization on bone microarchitecture, histology, and mechanical strength. For this study, Wistar rats (n= 38) were divided in 4 groups: 1) "Control OVX" (single dose of corn oil s.c. at day 5 of life and ovariectomy at day 100, n=9); 2) "Control SHAM" (n=9); 3) "Androgenized OVX"(single dose of TP 1.25 mg s.c. at day 5 of life and ovariectomy at day 100, n=10); and 4) "Androgenized SHAM" (n=10). Full characterization of estrous cycles and weight was performed during growth, and all animals were euthanized at day 180. Successful ovariectomy was confirmed by neglected levels of serum estradiol. Endpoints evaluated include bone micro CT (femur and spinal column), bone histology (number of osteoclasts and osteoblasts in the femur), and mechanical tests. The study was approved by the local Ethics Committee. At the end of the study (day 180), Androgenized OVX rats were heavier than the other three groups. MicroCT Analysis: Androgenized SHAM rats exhibited a significantly higher trabecular mass in the spine (BV/BT) (mean + SEM) 49.21 + 2.42 % versus Control SHAM 36.42 + 1.39 % (Student T-test p=0.001). Following ovariectomy, BV/BT in Androgenized OVX was 40.4 + 2.83 % against 20.34 + 1.85 % in Control OVX (Student T-test p=0.0003). Lumbar trabecular thickness(μm) was also higher in Androgenized OVX (p=0.0065) as well the Trabecular number (n/mm) (p=0.0003). A similar increase in trabecular mass was observed in the femur. Androgenized SHAM rats had a significant higher BV/BT (%), trabecular thickness(μm), and decreased trabecular separation ($p < 0.001$). However, a significant reduction in cortical bone (thickness) was noted (Student T-test p=0.001). A histological study of the distal femur of Androgenized SHAM rats also show a significantly increased number of osteoclasts and decreased number of osteoblasts than Control SHAM (0< 001). When submitted to the mechanical test, Androgenized Sham rats presented a decreased strength ($p<0.01$) in relation to its controls. After ovariectomy, there was a reduction in bone in all oophorectomized groups. However, differently than the vertebral bones, no differences regarding bone mechanical strength or stiffness as well microCT values, or bone histology parameters were noted in the femur of Control OVX or Androgenized OVX. Our results suggest that androgenization in a rodent model of PCOS leads, at the same time, to a generalized increase in trabecular (cancellous) bone mass (especially in the spine), associated with a reduced cortical bone mass and decreased strength of the femur.

Reproductive Endocrinology

OVARY, TESTES, AND IMPACT OF HORMONES ON METABOLIC FUNCTION

Analysis of BMP15-Induced Transcriptome in Human Granulosa Cells for the Identification of Novel Candidate Genes for Primary Ovarian Insufficiency

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