we compared AMH levels in early post-menarchal girls and regularly cycling adults. The rich phenotypic data available for this adolescent cohort (Sun 2019) was used to investigate further the relationship between AMH, LH, FSH, and sex steroids, and the propensity for anovulatory cycles (ANOV) in girls. 23 healthy girls (12.8–17.6 yrs;1.7±0.2 yrs post-menarche; 56% overweight/obese [OB]) underwent hormone measurements and pelvic ultrasounds during 2 consecutive menstrual cycles. Cycles were classified as ovulatory (OV) based on an LH and E2 peak and P4 >1.65 ng/mL (Sun 2019). AMH was measured in a random subset of samples (5x/subject) with the Ansh ultrasensitive ELISA. Maximum average ovarian volume (VOL) was calculated in the absence of a dominant follicle. Hormones were compared with data from 32 historic adult controls (18–34 yrs; 44% OB) with regular cycles (Lambert-Messerlian 2016). In adults, AMH was measured during the follicular and luteal phase of an OV (5x/subject) using the Ansh assay. AMH was compared among groups using a mixed model. AMH (in adults), LH (in both) and androgens (in girls) were natural log-transformed (ln) before analysis. 11 girls had 2 OV, 5 girls had 1 OV, and 5 girls had no OV; 2 could not be classified due to loss to follow-up. Girls had higher AMH than women (5.2 ± 0.3 vs. 3.3 ± 0.4 ng/mL; $p<0.01$) and girls with more OV tended to have lower AMH than those with ANOV (2 OV 4.5 ± 0.2, 1 OV 5.7 ± 1.1, 0 OV 6.8 ± 1.1 ng/mL; p=0.1). In girls, AMH correlated with ln_LH (r=0.4, p=0.02), ln_a'dione (r=0.4, p=0.04), ln_testosterone (r=0.5, p=0.02) and VOL (r=0.6, p=0.01) but not with FSH, E2, or BMI. In women, AMH correlated with E2 (r=-0.4, p=0.03) and not with ln_LH or BMI. Within-person variability in AMH was similar in girls and adults (CV 18%). During the early post-menarchal years, AMH levels exceed those of adults with OV, particularly among girls with ANOV, and correlate with LH and androgens. The finding of higher AMH in adolescents is consistent with previous studies demonstrating a peak in AF count during this stage of development. Investigation into how the normal ovary matures and is pruned of excess AFs, either by increased recruitment and growth or by atresia, may provide insights into the pathogenesis of PCOS, wherein follicles are arrested at the pre-antral and antral stage.

Bone and Mineral Metabolism

NEW INSIGHTS INTO PTH AND CALCIUM RECEPTOR SIGNALING

A Novel Ex Vivo Live-Cell Interrogative Assay of Human Parathyroid Tissue Reveals Distinct Mechanisms of Calcium Sensing Failure in Primary, Secondary, and Tertiary Hyperparathyroidism

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Disruption of calcium homeostasis is common to all forms of hyperparathyroidism (HPT), but the underlying biochemical mechanisms that distinguish the various forms of HPT pathology remain poorly characterized. We previously have observed that the kinetics and amplitude of CASR-mediated signaling vary significantly among parathyroid (PT) adenomas and found specific functional and gene expression profiles preferentially associated with increased risk of bone density loss. While these data established a clear connection between CASR activity and clinical phenotype, a direct comparison of the kinetics of PTH secretory behavior between normal and neoplastic intact human PT tissue has yet to be performed. Utilizing eucalcemic normal human organ donor tissues (n=3) as a reference standard, we examined a series of cryopreserved live PT tissue specimens obtained from patients with primary (n=9), secondary (n=12) and tertiary (n=5) HPT. PT tissue fragments matched for viability, mass, and cellular content were placed on permeable membranes and exposed to a series of extracellular calcium concentrations over equivalent time intervals of challenge and normocalcemic recovery to interrogate dynamic PTH secretory induction or suppression. As expected, normal tissue exhibited a sigmoid response curve indicative of allosteric calcium-mediated inhibition, with a mean EC50 of 0.95 mM (95% CI: 0.859–1.254). In contrast, the majority of primary HPT adenomas (n=6) displayed a concave response curve indicative of non-competitive inhibition, consistent with a primary sensing deficit, such as loss of CASR expression. Two distinct PTH secretory behaviors were observed in secondary HPT specimens. One subset (secondary type 1, n=4) retained a sigmoid response curve but with a modest EC50 increase (mean EC50=1.50 mM, 95% CI: 1.41–1.61) and maximal suppression similar to normal tissue, features reflective of competitive inhibition in response to elevated calcium. This pattern could indicate enhanced CASR antagonist activity relative to normal tissue. A second subset, (secondary type 2, n=8) demonstrated a large EC50 shift (mean EC50=2.46 mM; 95% CI: 1.844–2.621), a sigmoid response curve, and an elevated threshold of persistent PTH secretion at high calcium conditions. These parameters are suggestive of non-competitive inhibitory behavior, consistent with loss of a CASR-dependent downstream effector. Three of the primary HPT adenomas shared this response phenotype. Of the tertiary specimens, four matched the primary HPT adenoma pattern, while one exhibited secondary type 2 behavior. These results reveal a series of progressively attenuated dynamic response patterns, where PTH secretion becomes increasingly uncoupled from extracellular calcium sensing. These findings suggest that primary, secondary, and tertiary HPT arise through distinct mechanisms of calcium sensing failure.

Diabetes Mellitus and Glucose Metabolism

TYPE 1 DIABETES MELLITUS

Rare Case of 48 XXYY Syndrome with Suspected Type 1 Diabetes Mellitus

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Background: 48 XXYY syndrome is a rare aneuploidy characterized by the presence of an extra X and Y chromosome in males. Patients share features of Klinefelter